EXHIBIT O

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(54) **COLCHINE COMPOSITIONS AND METHODS**

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(63) Continuation of application No. 13/451,328, filed on Apr. 19, 2012, which is a continuation of application No. 13/175,062, filed on Jul. 1, 2011, which is a continuation of application No. 12/687,406, filed on Jan. 14, 2010, now Pat. No. 7,981,938, which is a continuation of application No. 12/545,377, filed on Aug. 21, 2009, now abandoned, which is a continuation of application No. 12/465,210, filed on May 13, 2009, now abandoned, and a continuation of application No. 12/407,980, filed on Mar. 20, 2009, now Pat. No. 7,964,647, which is a continuation of application No. 12/246,034, filed on Oct. 6, 2008, now abandoned.

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(51) **Int. Cl.**

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C07C 205/00	(2006.01)
C07C 207/00	(2006.01)

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See application file for complete search history.

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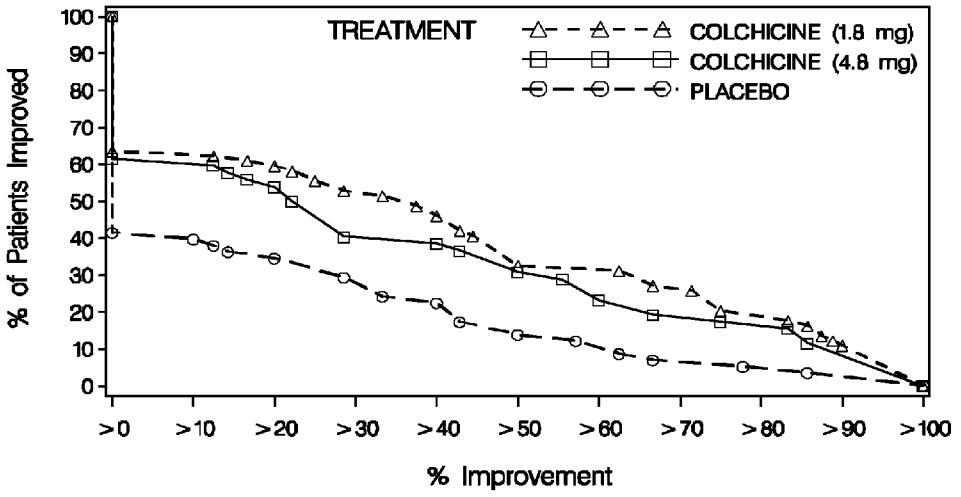
(57) **ABSTRACT**

Stable ultrapure colchicine compositions comprising ultrapure colchicine and a pharmaceutically acceptable excipient are described. The compositions can be tablets. Methods for preparing such compositions and methods of use are also disclosed. Methods of treating gout flares with colchicine compositions are also disclosed.

26 Claims, 1 Drawing Sheet


TREATMENT
COLCHICINE (1.8 mg)
COLCHICINE (4.8 mg)
PLACEBO
% of Patients Improved
100
90
80
70
60
50
40
30
20
10
0
>0
>10
>20
>30
>40
>50
>60
>70
>80
>90
>100
% Improvement

COLCHINE COMPOSITIONS AND METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/451,328, filed Apr. 19, 2012, which is a continuation of U.S. application Ser. No. 13/175,062, filed Jul. 1, 2011; which is a continuation of U.S. application Ser. No. 12/687,406, filed Jan. 14, 2010, now U.S. Pat. No. 7,981,938; which is a continuation of U.S. application Ser. No. 12/545,377, filed Aug. 21, 2009, now abandoned; which is a continuation of U.S. application Ser. No. 12/465,210, filed May 13, 2009, now abandoned, and a continuation of U.S. application Ser. No. 12/407,980, filed Mar. 20, 2009, now U.S. Pat. No. 7,964,647; which is a continuation of U.S. application Ser. No. 12/246,034, filed Oct. 6, 2008, now abandoned, which claims the benefit of U.S. Provisional Application Ser. No. 60/977,796 filed Oct. 5, 2007 and U.S. Provisional Application Ser. No. 61/090,965 filed Aug. 22, 2008; each of the above-named applications is hereby incorporated by reference in its entirety.

BACKGROUND

This application relates to colchicine compositions for therapeutic purposes, specifically ultrapure colchicine, and methods of making and using the colchicine compositions. Colchicine, chemical name (−)—N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[α]heptalen-7-yl]-acetamide, is a pale yellow powder soluble in water in 1:25 dilution.

Colchicine is an alkaloid found in extracts of certain plants such as *Colchicum autumnale* and *Gloriosa superba*. Colchicine arrests cell division in animals and plants. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid due to an overproduction of uric acid or a reduced ability of the kidney to get rid of uric acid. It is more common in males, postmenopausal women, and people with high blood pressure. Heavy alcohol use, diabetes, obesity, sickle cell anemia, and kidney disease also increase the risk. The condition may also develop in people who take drugs that interfere with uric acid excretion.

In gout, monosodium urate or uric acid crystals are deposited on the articular cartilage of joints, tendons and surrounding tissues due to elevated concentrations of uric acid in the blood stream. This provokes an inflammatory reaction of these tissues. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as swelling, redness, warmness, and stiffness in the affected joint. Low-grade fever may also be present. The patient usually suffers from two sources of pain. The crystals inside the joint cause intense pain whenever the affected area is moved. The inflammation of the tissues around the joint also causes the skin to be swollen, tender and sore if it is even slightly touched. For example, a blanket or even the lightest sheet draping over the affected area could cause extreme pain.

Acute gouty arthritis (alternatively referred to as a gout flare or a gout attack) is a sudden attack of pain in affected joints, especially in the feet and legs. Chronic gout involves repeated attacks of joint pain.

In acute gouty arthritis, symptoms develop suddenly and usually involve only one or a few joints. The big toe, knee, or ankle joints are most often affected. The pain frequently starts during the night and is often described as throbbing, crushing, or excruciating. The joint appears infected with signs of warmth, redness, and tenderness. The attacks of painful joints may go away in several days, but may return from time to time. Subsequent attacks usually last longer. Some people may progress to chronic gout (chronic gouty arthritis), while others may have no further attacks.

If several attacks of gout occur each year, it can lead to joint deformity and limited motion in joints. Uric acid deposits, called tophi, develop in cartilage tissue, tendons, and soft tissues. These tophi usually develop only after a patient has suffered from the disease for many years. Deposits also can occur in the kidneys, leading to chronic kidney failure.

Colchicine can be used for treating adults with acute gouty arthritis and pain in attacks of acute gouty arthritis, and also can be used beneficially for treating adults with chronic gout for prophylaxis of acute gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and the subsequent anti-inflammatory response. The anti-inflammatory effect of colchicine is relatively selective for acute gouty arthritis. However, other types of arthritis occasionally respond. It is neither an analgesic nor a uricosuric and will not prevent progression to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally experience. In some instances, non-steroidal anti-inflammatory drugs (NSAIDs) may also be prescribed to relieve pain and inflammation in acute gouty arthritis attacks. Strong painkillers, such as codeine, or corticosteroids may also be prescribed to relieve the pain.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

There remains a need for pure forms of colchicine having low levels of impurities for pharmaceutical use to minimize the potential for side effects in patients taking colchicine pharmaceutical products and to minimize the need for costly toxicity testing required for approval of pharmaceutical products comprising conventional colchicine having high levels of individual or total impurities. In particular, there is a need for stable compositions comprising ultrapure colchicine.

SUMMARY

Disclosed herein are colchicine compositions.

In one embodiment, the colchicine composition comprises ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities, specifically no more than about 2.0% total impurities, and a pharmaceutically acceptable excipient.

In another embodiment, the colchicine composition comprises ultrapure colchicine, wherein the ultrapure colchicine comprises no more than 3.0% total impurities, specifically no more than about 2.0% total impurities, a filler, a binder, and a disintegrant.

In yet another embodiment, the colchicine composition comprises about 0.6 mgA colchicine, about 12 to about 16 mg pregelatinized starch, about 20 to about 24 mg microcrystalline cellulose, about 3.9 to about 4.7 mg sodium starch gly-

colate, about 0.5 to about 0.7 mg magnesium stearate, and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities and no more than 0.42% N-deacetyl-N-formyl colchicine.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein the colchicine composition has 0.6 mgA colchicine, wherein a single dose of the 0.6 mgA colchicine composition has enhanced bioavailability as compared to a single dose of a pharmaceutical product comprising 0.5 mg colchicine after potency correction for colchicine.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein the colchicine composition has equivalent bioavailability when administered in a fed or a fasted state.

In an embodiment, the colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient, wherein administration of a single dose of the colchicine composition to a human provides a C_{max} between about 1.3 ng/mL and about 4.0 ng/mL, an AUC_{0-t} between about 4.4 ng-hr/mL and about 30.8 ng-hr/mL, or an AUC_{0-INF} between about 6.7 ng-hr/mL and about 27.8 ng-hr/mL.

Methods of making the colchicine compositions are also disclosed herein.

In an embodiment, the method comprises wet granulating ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% of total impurities, with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a disintegrant to obtain the composition.

In yet another embodiment, the method comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; mixing the milled granules with a disintegrant to obtain the composition; mixing the composition with a lubricant to obtain a tableting blend; and compressing the tableting blend to obtain a colchicine tablet.

Also disclosed herein are methods of making ultrapure colchicine.

In an embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to column chromatography to obtain a colchicine concentrate, distilling the colchicine concentrate to obtain a colchicine distillate, and crystallizing ultrapure colchicine from the colchicine distillate; wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In another embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; and crystallizing ultrapure colchicine from the colchicine distillate in ethyl acetate; wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In still another embodiment, the method comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; crystallizing a purified colchicine from the colchicine distillate in ethyl acetate; washing the purified colchicine with ethyl acetate to obtain a washed purified colchicine; and drying the washed purified colchicine to obtain ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

Also disclosed are methods of treating a patient with the colchicine compositions.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine.

In an embodiment, the method comprises administering less than about 2 mg of colchicine to a patient over a period of about one hour, wherein the patient is experiencing an acute gouty arthritis attack.

In an embodiment, the method comprises administering to a human experiencing an acute gouty arthritis attack a colchicine composition, wherein the composition is effective to provide a colchicine plasma concentration profile having an area under the plasma colchicine concentration curve from time 0 to infinity (AUC_{0-INF}) of about 34.2 ng-hr/mL to about 74.1 ng-hr/mL, an area under the plasma colchicine concentration curve from time 0 to time t (AUC_{0-t}) of about 28.8 ng-hr/mL to about 58.9 ng-hr/mL, or a maximum plasma colchicine concentration (C_{max}) of about 3.2 ng/mL to about 11.4 ng/mL for a maximum total dose of about 1.8 mg colchicine.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the dosing regimen is effective to provide an area under the plasma colchicine concentration curve from time 0 to infinity (AUC_{0-INF}) of about 34.2 ng-hr/mL to about 74.1 ng-hr/mL, an area under the plasma colchicine concentration curve from time 0 to time t (AUC_{0-t}) of about 28.8 ng-hr/mL to about 58.9 ng-hr/mL, or a maximum plasma colchicine concentration (C_{max}) of about 3.2 ng/mL to about 11.4 ng/mL.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the dosing regimen is effective to provide a colchicine plasma concentration profile which has a maximum plasma colchicine concentration (C_{max}) which is at least 80% of plasma C_{max} provided by a dosing regimen of two dosage forms, followed by one dosage form about every hour later for 6 hours.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein the odds of a patient being a responder to the dosing regimen are not statistically different from the odds of being a responder to a second dosing regimen consisting of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form every hour for 6 hours, wherein a responder is a patient obtaining a ≧50% improvement in pain at 24 hours

after the first dose, without taking an additional active agent for reducing pain of the acute gouty arthritis attack.

In an embodiment, the method comprises administering a dosing regimen to a patient having an acute gouty arthritis attack, wherein the dosing regimen consists of two colchicine dosage forms at the onset of the acute gouty arthritis attack, followed by one colchicine dosage form in about one hour, wherein a colchicine dosage form comprises about 0.6 mgA colchicine, wherein in a randomized, placebo-controlled study of the dosing regimen in patients with an acute gouty arthritis attack, the fraction of patients that experienced a given % improvement in pain at 24 hrs after first dose is shown in FIG. **1**.

These and other embodiments, advantages and features of the present invention become clear when detailed description and examples are provided in subsequent sections.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the fraction of all patients improved at 24 hrs post-first dose of colchicine, regardless of pain rescue, as a function of the percent improvement in pain determined in the study of Example 3.

DETAILED DESCRIPTION

Disclosed herein are compositions comprising ultrapure colchicine and a pharmaceutically acceptable excipient. Herein, "ultrapure colchicine" means colchicine comprising no more than about 3.0% of total impurities, measured chromatographically as described below, specifically the ultra pure colchicine comprises no more than about 2.0% of total impurities, more specifically no more than about 1.0% of total impurities, or even more specifically no more than about 0.5% of total impurities. In some embodiments, the ultrapure colchicine comprises no more than about 0.10% of N-deacetyl-N-formyl colchicine, measured chromatographically. In some embodiments, the ultrapure colchicine is purified from a botanical source. Methods of making ultrapure colchicine and the compositions comprising the ultrapure colchicine, methods of treating various conditions using the compositions. Dosing regimens are also disclosed.

Not wishing to be bound by theory, it is postulated that the properties of colchicine as an antimitotic agent (e.g. its tubulin binding properties) or its effects on Pgp transporter properties provide the therapeutic effects of colchicine described herein. The methods described herein therefore also contemplate the use of an antimitotic agent with at least one pharmaceutically acceptable excipient. An antimitotic agent can be a drug that prevents or inhibits mitosis, or cell division.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to") unless otherwise noted.

An "active agent" means a compound (including for example, colchicine), element, or mixture that when administered to a patient, alone or in combination with another compound, element, or mixture, confers, directly or indirectly, a physiological effect on the patient. The indirect physiological effect may occur via a metabolite or other indirect mechanism. When the active agent is a compound, then salts, solvates (including hydrates), and co-crystals of the free compound or salt, crystalline forms, non-crystalline forms, and any polymorphs of the compound are contemplated herein. Compounds may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g., asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, all optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example, a chiral HPLC column. All forms are contemplated herein regardless of the methods used to obtain them.

"Bioavailability" means the extent or rate at which an active agent is absorbed into a living system or is made available at the site of physiological activity. For active agents that are intended to be absorbed into the bloodstream, bioavailability data for a given formulation may provide an estimate of the relative fraction of the administered dose that is absorbed into the systemic circulation. "Bioavailability" can be characterized by one or more pharmacokinetic parameters.

"Bioequivalence" or "equivalent bioavailability" means the absence of a significant difference in the rate or extent to which the active agent in pharmaceutical equivalents or pharmaceutical alternatives is absorbed into a living system or is made available at the site of physiological activity or the absence of a significant difference in the rate or extent to which the active agent in a pharmaceutical composition is absorbed into a living system or is made available at the site of physiological activity when administered by two different methods (e.g., dosing under non-fasted versus fasted conditions). Bioequivalence can be determined by comparing in vitro dissolution testing data for two dosage forms or two dosing conditions or by comparing pharmacokinetic parameters for two dosage forms or two dosing conditions.

In some embodiments, two products (e.g. an inventive composition and COL-PROBENECID®) or two methods (e.g., dosing under fed (non-fasted) versus fasted conditions) are bioequivalent if the ratio of the geometric mean of logarithmic transformed $AUC_{0-\infty}$, AUC_{0-t}, or C_{max} for the two products or two methods is about 0.80 to about 1.25; specifically if the 90% Confidence Interval (CI) limit for the ratio of the geometric mean of logarithmic transformed $AUC_{0-\infty}$, AUC_{0-t}, or C_{max} for the two products or two methods is about 0.80 to about 1.25; more specifically if the ratios of the geometric mean of logarithmic transformed $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for the two products or two methods are about 0.80 to about 1.25; yet more specifically if the 90% Confidence Interval (CI) limits for the ratios of the geometric mean of logarithmic transformed $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for the two products or two methods are about 0.80 to about 1.25.

"Colchicine therapy" refers to medical treatment of a symptom, disorder, or condition by administration of colchicine. Colchicine therapy can be considered optimal when effective plasma levels are reached when required. In addition, peak plasma values (C_{max}) should be as low as possible so as to reduce the incidence and severity of possible side effects.

"Conventional colchicine" means colchicine comprising more than 3% but no more than about 5.0% total impurities, measured chromatographically as described below, and comprising more than about 0.10% of N-deacetyl-N-formyl colchicine.

A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, injections, suspensions, liquids, emulsions, creams, ointments, suppositories, inhalable forms, transdermal forms, and the like.

"Dosing regimen" means the dose of an active agent taken at a first time by a patient and the interval (time or symptomatic) at which any subsequent doses of the active agent are taken by the patient. The additional doses of the active agent can be different from the dose taken at the first time.

A "dose" means the measured quantity of an active agent to be taken at one time by a patient.

"Efficacy" means the ability of an active agent administered to a patient to produce a therapeutic effect in the patient.

As used herein, the term "mgA" refers to milligrams of the active colchicine, or the free base of colchicine, after compensating for the potency of the batch of colchicine (i.e., after compensating for impurities, including solvents, and salts in the colchicine). For example, 0.612 mg of an ultrapure colchicine free base having a total impurity of 2 wt % (thus a purity of 98 wt %) contains 0.6 mgA (0.612 mg×0.98=0.6 mgA) of colchicine.

An "oral dosage form" means a unit dosage form for oral administration.

A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient.

"Pharmaceutically acceptable" means that which is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" includes derivatives of colchicine, wherein the colchicine is modified by making acid or base addition salts thereof, and further refers to pharmaceutically acceptable solvates, including hydrates, and co-crystals of such compounds and such salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid addition salts of basic residues such as amines; alkali or organic addition salts of acidic residues; and the like, and combinations comprising one or more of the foregoing salts. The pharmaceutically acceptable salts include non-toxic salts and the quaternary ammonium salts of the colchicine. For example, non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; other acceptable inorganic salts include metal salts such as sodium salt, potassium salt, cesium salt, and the like; and alkaline earth metal salts, such as calcium salt, magnesium salt, and the like, and combinations comprising one or more of the foregoing salts. Pharmaceutically acceptable organic salts includes salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC—$(CH_2)_n$—COOH where n is 0-4, and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, asparaginate, glutamate, and the like; and combinations comprising one or more of the foregoing salts; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N' dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, asparaginate, glutamate, and the like; and combinations comprising one or more of the foregoing salts. All forms of such derivatives of colchicine are contemplated herein, including all crystalline, amorphous, and polymorph forms. Specific colchicine salts include colchicine hydrochloride, colchicine dihydrochloride, and co-crystals, hydrates or solvates thereof.

"Pharmacokinetic parameters" describe the in vivo characteristics of an active agent (or a metabolite or a surrogate marker for the active agent) over time, such as plasma concentration (C), C_{max}, C_n, C_{24}, T_{max}, and AUC. "C_{max}" is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. "C_{min}" is the measured plasma concentration of the active agent at the point of minimum concentration. "C_n" is the measured plasma concentration of the active agent at about n hours after administration. "C_{24}" is the measured plasma concentration of the active agent at about 24 hours after administration. The term "T_{max}" refers to the time at which the measured plasma concentration of the active agent is the highest after administration of the active agent. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-\infty}$ or AUC_{0-INF} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_e or K_{el}, the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{el}$; CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_∞; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_\infty \times K_{el}$).

"Adverse event" means any untoward medical occurrence in a patient administered an active agent and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the active agent, whether or not considered related to the active agent.

"Side effect" means a secondary effect resulting from taking an active agent. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically diarrhea; abdominal pain with cramps; nausea; and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Determining that a patient experiences an adverse side effect can be performed by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Ultrapure colchicine comprising low levels of individual impurities or total impurities is highly desirable as compared to conventionally available forms of colchicine. Currently, commercially available forms of colchicine often comprise high levels of impurities. Depending on the source or the preparation process, colchicine may comprise some or all of the common impurities shown in Table 1.

TABLE 1

Common Impurities	Chemical Name	Other common name
Impurity A	N-[(7S,12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]formamide	N-deacetyl-N-formyl colchicine
Impurity B	(−)-N-[(7S,12aR)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-acetamide	Conformational isomer
Impurity C	N-[(7S,7bR,10aS)-1,2,3,9-tetra-methoxy-8-oxo-5,6,7,7b,8,10a-hexahydrobenzo[a]cyclopenta[3,4]cyclo-buta[1,2-c]cyclohepten-7-yl]-acetamide	β-Lumicolchicine
Impurity D	N-[(7S,12aS)-3-(β-D-glucopyranosyloxy)-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetra-hydrobenzo[a]heptalen-7-yl]-acetamide	Colchicoside
Impurity E	N-[(7S,12aS)-3-hydroxy-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-acetamide	3-O-demethyl colchicine
Impurity F	N-[(7S,12aS)-10-hydroxy-1,2,3-trimethoxy-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]acetamide	Colchiceine

In addition to the common impurities listed above, colchicine may also comprise N-[(7S,12aS)-2-hydroxy-1,3,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide ("2-O-demethyl colchicine") impurity. Some analytical methods cannot differentiate 2-O-demethyl colchicine from 3-O-demethyl colchicine.

In addition to the common impurities listed above, colchicine may also comprise other structurally unidentified impurities. In fact, conventional forms of colchicine may comprise as much as 5% of total impurities, determined chromatographically as described below. Such high levels of impurities in conventional colchicine pose several problems. The impurities may cause side effects in patients taking dosage forms comprising conventional colchicine. For example, N-deacetyl-N-formyl-colchicine (Impurity A, also known as Gloriosine) is tumorigenic and has been studied as an anticancer agent. Therefore reduction in the level of N-deacetyl-N-formyl colchicine found in convention colchicine is highly desirable. Additionally, high levels of impurities can also pose a regulatory challenge for pharmaceutical companies using conventional colchicine in products. For a pharmaceutical product comprising an active agent, the United States Food and Drug Administration (FDA) requires "qualification" or toxicity information for any impurity that is greater than the International Conference on Harmonization (ICH) qualification threshold of 0.15% per individual impurity in the active agent substance or 1.0% in the dosage form. Thus, there is a regulatory benefit for a pharmaceutical company to market pharmaceutical products comprising active agents comprising low levels of individual impurities or total impurities in the active agent substance as well as in the dosage form. As a result, for a pharmaceutical composition comprising colchicine, it is in the best interest of both the pharmaceutical company and the patient that impurities be minimized, if possible, in the colchicine and in colchicine compositions or dosage forms.

The ultrapure colchicine disclosed herein comprises no more than (NMT) about 3.0%; specifically NMT about 2.0%, or more specifically, NMT about 1.0%, or even more specifically NMT about 0.5% of total impurities. In one embodiment, "total impurities" includes the common impurities, Impurities A through F, as well as all structurally unidentified impurities eluting within 1.5 times the retention time of colchicine using an HPLC method as described in more detail below. In another embodiment, other HPLC and UPLC methods, for example, as described in more detail below, can be used to quantify the level of total impurities.

The ultrapure colchicine may also comprise low levels of individual impurities. In one embodiment, the ultrapure colchicine comprises NMT about 2.0%, specifically NMT about 1.5%; more specifically NMT about 1.0%; or yet more specifically, NMT about 0.5%, or even more specifically, NMT about 0.15%, or still more specifically, NMT about 0.10%, of any individual impurity. The impurity can be Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, or an unidentified impurity.

In an embodiment, the ultrapure colchicine comprises no more than (NMT) about 3.0% total impurities and NMT about 0.10% N-deacetyl-N-formyl colchicine.

In another embodiment, the ultrapure colchicine comprises NMT about 3.0% total impurities; NMT about 0.1% per individual impurity of Impurity A, Impurity C, Impurity D, and Impurity E; NMT about 0.15% Impurity F; and NMT about 2.0% of Impurity B.

Not wishing to be bound by theory, it is postulated that the conformational isomer, Impurity B, is in equilibrium with the active colchicine such that even after purification of the colchicine to about 0.5% Impurity B, the purified colchicine re-equilibrates to a level of Impurity B around about 1% to about 1.3%.

The level of an individual impurity or of total impurities in colchicine may be determined by any suitable analytical method known in the art. In one embodiment, the impurity levels are determined using a high performance liquid chromatography (HPLC) assay, for example, the HPLC method described in the Colchicine Official Monograph USP30/NF25, herein fully incorporated by reference.

Exemplary conditions for HPLC or ultra performance liquid chromatography (UPLC) assays that can be used for the impurity analysis of colchicine or of a colchicine pharmaceutical product are listed in Table 2.

TABLE 2

Exemplary HPLC Conditions For Colchicine Purity Analysis

	USP30/NF25 Colchicine Official Monograph Method	HPLC Method	UPLC Method
Mobile phase	0.5 Molar KH_2PO_4 in Methanol:Water (65:45, v:v), pH adjusted to 5.5 with H_3PO_4	pH 7.2 10 mM Phosphate Buffer:methanol (MeOH) Gradient	pH 4.5 Ammonium Acetate Buffer:MeOH Gradient
Column	Octylsilyl silica gel, 4.6 mm × 25 cm, 5 micron	Zorbax SBC(18) 4.6 × 250 mm	Acquity GEH C18 2.1 × 100 mm, 1.7 um
Flow rate	1.0 mL/min	1.0 mL/min	0.25 mL/min
Column Temp	Ambient	Ambient	30 C. +/− 2 C.

TABLE 2-continued

Exemplary HPLC Conditions For Colchicine Purity Analysis

	USP30/NF25 Colchicine Official Monograph Method	HPLC Method	UPLC Method
Detection	254 nanometers (nm)	246 nm	246 nm
Injection volume	20 microliters (uL)	75 uL	7 uL
Sample Conc.	0.006 mg/mL	0.120 mg/ml	0.012 mg/ml
Run time	15 minutes (min)	46 min	25 min

When using one of the above HPLC conditions in Table 2 for colchicine purity analysis, the relative retention time (RRT) of an impurity can be calculated by the following formula:

RRT of an impurity=of the impurity/RT of colchicine,

where RT stands for retention time of the impurity or the colchicine at the particular conditions used in the assay.

In one embodiment, using the HPLC method in Table 2, the retention time (RT) of colchicine is about 7 minutes and the relative retention times (RRTs) of the common impurities eluting within 1.5 times the retention time for colchicine are listed in Table 2A:

TABLE 2A

Relative Retention Times (RRTs) of the Common Impurities

Impurity ID	RRT
N-deacetyl-N-formyl colchicine - Impurity A	0.94
Conformational isomer - Impurity B	0.8
β-Lumicolchicine - Impurity C	1.2
Colchicoside - Impurity D	0.4
3-O-demethyl colchicine - Impurity E	0.7

In one embodiment, the percent of a particular impurity is calculated by dividing the response (peak area) of the impurity peak by the sum of all responses (total peak area of all peaks, including the colchicine peak and all common and unidentified impurity peaks) eluting within 1.5 times the retention time for colchicine in the HPLC assay and multiplying the result by 100%.

In one embodiment, the level (%) of total impurities is calculated by dividing the sum of responses of any peaks other than that due to colchicine eluting within 1.5 times the retention time for colchicine by the sum of all responses eluting in the HPLC assay and multiplying the result by 100%.

An additional HPLC method for determining the level of impurities other than Impurity F in colchicine or in colchicine pharmaceutical products has been developed and validated for use as an alternative to the methods in Table 2 above. The method is shown in Table 3A below.

TABLE 3A

Quantitative HPLC Method for determining all impurities other than impurity F in colchicine and colchicine pharmaceutical products.

	Quantitative HPLC Method for colchicine and colchicine products.
Mobile phase	pH 4.5 Ammonium Acetate Buffer:methanol Gradient
Column	Waters XBridge C18, 250 mm × 4.6 mm, 5 μm particle size
Flow rate	0.9 mL/min
Column Temp	10 ± 3.5 C. (for column) /10 ± 2 C. (for sample)
Detection	246 nm
Injection volume	75 μL
Sample Conc.	0.16 mg/ml
Run time	60 min

In the quantitative HPLC method of Table 3A, the retention time (RT) of colchicine is about 24 minutes and the relative retention times (RRTs) of the common impurities for colchicine are listed in Table 3B:

TABLE 3B

Relative Retention Times (RRTs) of the Common Impurities

Impurity ID	RRT
N-deacetyl-N-formyl colchicine - Impurity A	0.93
Conformational isomer - Impurity B	0.82
β-Lumicolchicine - Impurity C	1.76
Colchicoside - Impurity D	0.18
3-O-demethyl colchicine - Impurity E	0.52
2-O-demethyl colchicine	0.54
Gamma-Lumicolchicine	1.37

The percentage of individual impurities in the sample solution is calculated as follows:

$$\%\ \text{Impurity} = \frac{r_i}{r_s} \times \frac{W_S\ (\text{mg})}{100\ \text{mL}} \times \frac{6.0\ \text{mL}}{100\ \text{mL}} \times \frac{2.0\ \text{mL}}{100\ \text{mL}} \times P \times \left(\frac{100 - \%RS_S - \%W_S}{100}\right) \times \frac{200\ \text{mL}}{SW\ (\text{mg}) \times \left(\frac{100 - \%RS_u - \%W_u}{100}\right)} \times \frac{100\%}{RRF}$$

Where:

r_s=The area response of the Colchicine peak in the Working Standard Solution.

r_i=The area response of the impurity peak in the Sample Solution

P=% Purity of the Colchicine Reference Standard divided by 100%.

SW=Weight of Sample taken for Sample Preparation

W_s=Weight of Colchicine in the Stock Standard Solution

RRF=Relative Response Factor for specified and unspecified impurities, 1.0

% $RS_{s/u}$=Percent of Residual Solvents in the Colchicine Standard/Sample

% $W_{s/u}$=% Water in the Colchicine Standard/Sample

To date, the impurity colchiceine (Impurity F or 10-O-Demethyl Colchicine "10-DMC") has been typically analyzed by a qualitative colorimetric test described in the Colchicine Official Monograph USP30/NF25 using ferric chloride solution, rather than chromatographically. The standard for acceptable levels of Impurity F has been absence of production of a definite green color in a solution of colchicine.

However, a chromatographic method has been developed for the determination of Impurity F (Colchiceine or 10-O-Demethyl Colchicine "10-DMC"). The chromatographic conditions are as follows:

TABLE 3C

HPLC parameters for Colchiceine determination

HPLC System:	HPLC equipped with a pump, auto sampler, variable wavelength detector and a suitable data acquisition system.
Column:	Phenomenex Gemini C18 150 mm × 4.6 mm 5 µm, 110Å
Detection:	245 nm
Flow Rate:	About 1.5 mL/min
Injection Volume:	50 µL
Temperature:	Column: 10° C. ± 3.5° C. Sample: 5° C. ± 2° C.
Needle Rinse Setting:	Double
Needle Wash:	Water:Acetonitrile (50:50)
Digital Filter Response:	1.0
Sampling Rate:	5.0
Resolution:	1.2
Mobile Phase:	pH 4.5 Buffer Solution:Acetonitrile (75:25)
Run Time:	About 7 minutes for Standard About 20 minutes for first Blank and Samples

The LQL level for 10-DMC in this method is 0.776304 µg/mL. The amount of 10-DMC expressed in percent of Colchicine is calculated as follows:

$$\%\ \text{Purity} = \frac{r_i}{r_s} \times \frac{W_S\ (\text{mg}) \times P}{400\ \text{mL}} \times \left(\frac{100 - \%RS_s - \%W_S}{100}\right) \times \frac{3.0\ \text{mL}}{100\ \text{mL}} \times \frac{50\ \text{mL}}{W_u\ (\text{mg}) \times \left(\frac{100 - \%RS_u - \%W_u}{100}\right)} \times \frac{100\%}{RRF}$$

Where:

r_i=The peak area response of 10-DMC in the Sample Solution

r_s=The peak area response of Colchicine in the Working Standard Solution

W_s=The weight of Colchicine in the Stock Standard Preparation

W_u=The weight of Colchicine in the Sample Preparation

P=Standard purity factor expressed as labeled (% Purity/100)

$\%RS_{s/u}$=Percent of Residual Solvents in the Colchicine Standard/Sample

$\%W_{s/u}$=% Water in the Colchicine Standard/Sample

RRF=Relative response factor for 10-DMC=0.88

Ultrapure colchicine may be obtained by various purification methods starting from colchicine-containing botanical extracts, conventional colchicine, or other partially-purified forms of colchicine. In some embodiments, the colchicine is purified from a botanical source. The botanical source can be any capable of providing colchicine, conventional or ultrapure, in quantities suitable for commercial pharmaceutical product manufacture.

The literature from 1884-1997 on methods of isolation and purification of colchicine from various botanic sources, including for example *C. autumnale* corms or leaves and species of Gloriosa has been reviewed. (Kiselev & Yavich, 1991, "METHODS OF ISOLATING ALKALOIDS OF THE COLCHICINE SERIES"; Plenum Publishing Co., English translation of article from Khimiya Prirodnykh Soedinenii, No. 5, pp. 592-600, September-October, 1990.). Kiseleve & Yavich also review reports in the literature of impurities detected in colchicine stored for various times, as follows. In an article published in 1944 it was reported that chromatography of colchicine corresponding to the requirements of the USP of that time showed the presence of 5% of impurities and various amount of individual impurities. An article published in 1952 reported that colchicine meeting the requirements of the USP contained about 4% of 3-demethylcolchicine. A 1953 article reported 1.5% of N-formyldeacetylcolchicine isolated and the presence of other accompanying alkaloids in a pharmacopeial sample of colchicine. An investigation of a commercial sample by high-resolution liquid chromatography, published in 1986, reported finding 93.4% of colchicine, 2.9% of N-formyldeacetylcholchicine, 1.8% of 17-hydroxycolchicine, and 0.84% of an unknown substance.

Walaszik et al. describes a process of incorporating carbon 14 into *C. autumnale* plants and isolating radioactive colchicine from the radioactive plants (See Walaszik et al., Science (1952) 116:225-227). However, the level of impurities in the isolated radioactive colchicine is not disclosed.

The purification methods disclosed herein produce ultrapure colchicine comprising very low levels of total impurities or individual impurities. In one embodiment, ultrapure colchicine may be obtained from conventional colchicine obtained commercially or produced using solvent extraction of appropriate botanic material as described in more detail below.

In one embodiment, conventional colchicine may be obtained by isolating colchicine from a colchicine chloroform extract. The extract is washed with a mixture of purified water, sodium hydroxide solution, sodium chloride solution and acetic acid. The washed extract is filtered and the resulting concentrate is distilled in two steps, first using methanol, and second using ethyl acetate. The resulting distillate is crystallized. Ethyl acetate can be used to isolate and wash the crystallized colchicine, which is then dried to yield conventional colchicine. The conventional colchicine comprises more than about 3.0% but no more than 5% total impurities.

The conventional colchicine may be used directly in a colchicine composition comprising a pharmaceutically acceptable excipient. It may also be used for further purification to obtain ultrapure forms of colchicine.

In one embodiment of a method of making ultrapure colchicine, the conventional colchicine may be subjected to column chromatography to obtain a purified colchicine concentrate, distilling the purified colchicine concentrate to obtain a colchicine distillate, and crystallizing ultrapure colchicine from the colchicine distillate. The method can further comprise washing the crystallized ultrapure colchicine with a solvent and drying. The ultrapure colchicine comprises no more than about 3.0% of total impurities.

In one embodiment, the column chromatography is carried out using methylene chloride as solvent on a column of neutral alumina. Other solvents or chromatographic media may be used, provided that impurities are removed from the conventional colchicine to the desired level. In another embodiment, distillation of the purified colchicine concentrate is carried out using ethyl acetate. Other organic solvents can be used, provided that impurities are removed from the purified colchicine concentrate. In yet another embodiment, the solvent used to wash the crystallized ultrapure colchicine is ethyl acetate.

In another embodiment, a method of making ultrapure colchicine comprises subjecting colchicine comprising more than about 3.0% total impurities to neutral alumina column chromatography to obtain a colchicine concentrate; distilling the colchicine concentrate with ethyl acetate to obtain a colchicine distillate; crystallizing a purified colchicine from the colchicine distillate in ethyl acetate; washing the purified colchicine with ethyl acetate to obtain a washed purified

colchicine; and drying the washed purified colchicine to obtain ultrapure colchicine, wherein the ultrapure colchicine comprises no more than about 3.0% total impurities.

In one embodiment, the ultrapure colchicine obtained in any of the above methods comprises no more than about 2.0% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 1.5% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 1.0% total impurities. In another embodiment, the ultrapure colchicine comprises no more than about 0.5% total impurities. In yet another embodiment, the ultrapure colchicine comprises no more than about 0.5% per individual impurity of Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, or Impurity F. In still another embodiment, the ultrapure colchicine comprises no more than about 0.15% per individual impurity of Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F. In another embodiment, the ultrapure colchicine comprises no more than about 1.0% of total unidentified impurities. In yet another embodiment, the ultrapure colchicine comprises no more than about 0.5% of total unidentified impurities. In yet another embodiment, the ultrapure colchicine comprises no more than 1.0% of Impurity B, and no more than 0.1% per individual impurity of any of Impurity A, Impurity C, Impurity D, Impurity E, and Impurity F.

The above methods of making ultrapure colchicine are only examples of suitable methods for its preparation.

The colchicine compositions disclosed herein comprise colchicine and a pharmaceutically acceptable excipient. In one embodiment, the colchicine composition comprises 0.1 wt % to 10 wt % colchicine, specifically 0.1 wt % to 5 wt % colchicine. In one embodiment, the colchicine in the colchicine compositions is ultrapure colchicine. The compositions comprising ultrapure colchicine are stable and provide enhanced safety to patients taking the compositions because the patients are ingesting fewer impurities. In particular, the colchicine compositions contain substantially lower levels of the tumorigenic compound N-deacetyl-N-formyl colchicine.

The pharmaceutically acceptable excipient in the colchicine composition may be a filler (or diluent), a binder, a disintegrant, a lubricant, or a combination comprising two or more of the foregoing excipients.

In one embodiment, the pharmaceutically acceptable excipient comprises a filler. Exemplary fillers may be one or more compounds which are capable of providing compactability and good flow. Exemplary fillers include microcrystalline cellulose, starch, lactose, sucrose, glucose, mannitol, maltodextrin, sorbitol, dextrose, silicic acid, dibasic calcium phosphate, or a combination comprising at least one of the foregoing fillers. Exemplary lactose forms include lactose monohydrate, NF (Fast Flo), lactose spray-dried monohydrate, and lactose anhydrous. Exemplary microcrystalline cellulose (MCC) include, for example, AVICEL® PH101 and AVICEL® PH102, which are commercially available from FMC Biopolymer, Philadelphia, Pa. Exemplary dibasic calcium phosphates include dihydrated and anhydrous dibasic calcium phosphates. In one embodiment, the filler is a combination of microcrystalline cellulose and lactose monohydrate, NF (fast flo).

When present, the amount of the filler in the composition may be about 10 wt % to about 99 wt %, or more specifically, about 30 wt % to about 90 wt %, or even more specifically, about 50 wt % to about 90 wt %, or still more specifically, about 70 wt % to about 85 wt %, based on the total weight of the composition. In one embodiment, the total amount of the filler is about 82 wt %, based on the total weight of the composition.

In one embodiment, the pharmaceutically acceptable excipient comprises a binder. Binders may be used to impart cohesive qualities to a formulation, for example, a tablet formulation, and thus ensure that the tablet remains intact after compaction. Exemplary binders include starches (for example, Starch 1500® or pregelatinized starch), alginates, gelatin, carboxymethylcellulose, sugars (for example, sucrose, glucose, dextrose, and maltodextrin), polyethylene glycol, waxes, natural and synthetic gums, polyvinylpyrrolidone, and cellulosic polymers (for example, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, and hydroxyethyl cellulose) and combinations comprising one or more of the foregoing binders. In one embodiment, the binder is starch, or more specifically, pregelatinized starch.

When present, the amount of the binder may be about 10 wt % to about 99 wt %, or more specifically, about 10 wt % to about 50 wt %, or even more specifically, about 10 wt % to about 20 wt %, based on the total weight of the composition. In one embodiment, the amount of the binder is about 14 wt %, based on the total weight of the composition.

In another embodiment, the pharmaceutically acceptable excipient comprises a disintegrant. Disintegrants are used to facilitate disintegration or "breakup" of a composition, for example, a tablet, after administration. Exemplary disintegrants include sodium starch glycolate, sodium croscarmellose (cross-linked carboxy methyl cellulose), crosslinked polyvinylpyrrolidone (PVP-XL), anhydrous calcium hydrogen phosphate, agar-agar, potato or tapioca starch, alginic acid, or a combination comprising one or more of the foregoing disintegrants.

When present, the disintegrant may be present in an amount of about 0.1 to 30 wt %, or more specifically, about 1 to 20 wt %, or even more specifically, about 1 to 10 wt %, based on the total weight of the composition. In one embodiment, the amount of the disintegrant is about 4.5 wt %, based on the total weight of the composition.

In another embodiment, the pharmaceutically acceptable excipient comprises a lubricant. Generally, a lubricant is added just before tableting, and is mixed with the rest of the composition for a minimum period of time to obtain good dispersal. Exemplary lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic acid, talc, glyceryl behenate, polyethylene glycol, polyethylene glycol, polyethylene oxide, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, or a combination comprising one or more of the foregoing lubricants. In one embodiment, the lubricant is magnesium stearate, calcium stearate, or zinc stearate.

When present, the lubricant may be present in an amount of about 0.01 wt % to about 10 wt %, or more specifically, about 0.1 wt % to about 5 wt %, or even more specifically, about 0.1 wt % to about 1 wt %, based on the total weight of the composition. In one embodiment, the amount of the lubricant is about 0.6 wt %, based on the total weight of the composition.

If desired, the composition may optionally comprise small amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, or pH buffering agents, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, and polyoxyethylene sorbitan fatty acid esters.

In one embodiment, a composition comprises an ultrapure colchicine, wherein the ultrapure colchicine comprises no more than 3.0% of total impurities, a filler, a binder, and a disintegrant.

In another embodiment, a colchicine composition comprises about 0.6 mgA colchicine; about 14 mg pregelatinized starch; about 22 mg microcrystalline cellulose; about 4.3 mg sodium starch glycolate; about 0.6 mg magnesium stearate; and an amount of lactose monohydrate such that the colchicine composition has a total weight of about 100 mg. In one embodiment, the colchicine in the colchicine composition is ultrapure colchicine.

In an embodiment, a colchicine composition comprises colchicine; and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities, specifically no more than about 3.0% total impurities, more specifically no more than about 2.0% total impurities, or yet more specifically no more than about 1.0% total impurities. In some of these embodiments, specific limitations on the levels of individual impurities are also met by the colchicine composition. In addition to containing no more than a particular maximum level of total impurities, the colchicine composition can comprise not more than about 0.42% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% Impurity B; specifically not more than about 0.2% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 1.5% Impurity B; and more specifically not more than about 0.15% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 1.1% Impurity B. In one embodiment the colchicine composition comprises no more than 3.5% total impurities, no more than 0.42% Impurity A, and no more than 2.0% Impurity B. The pharmaceutically acceptable excipient can be one or more discussed previously herein.

In one embodiment, a colchicine composition comprises colchicine and a pharmaceutically acceptable excipient; wherein the colchicine composition comprises no more than about 3.5% total impurities. In some embodiments, the colchicine composition comprises ultrapure colchicine and total impurities in the ultrapure colchicine comprise no more than about 3.0%, or specifically no more than about 2.0%, or more specifically no more than about 1.5%, or yet more specifically, no more than about 1.0%. In addition to containing no more than a particular maximum level of total impurities, the ultrapure colchicine in the colchicine composition can comprise not more than about 0.15% Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% Impurity B; specifically not more than about 0.10% Impurity A, Impurity C, Impurity D, or Impurity E; not more than about 0.15% Impurity F, and not more than about 1.5% Impurity B. In one embodiment the colchicine composition comprises ultrapure colchicine comprising no more than 0.10% Impurity A, no more than about 0.15% Impurity F, and no more than 2.0% Impurity B. The pharmaceutically acceptable excipient can be one or more discussed previously herein.

In one embodiment, a colchicine composition comprises colchicine; a filler; a binder; and a disintegrant; wherein the colchicine composition comprises no more than about 3.5% total impurities. In some embodiments, the colchicine composition comprises ultrapure colchicine and total impurities in the composition comprise no more than about 3.5%, or specifically no more than about 3.0%, more specifically no more than about 2.0%, or yet more specifically, no more than about 1.0%; with individual impurity levels of not more than about 0.42% for Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% for Impurity B, or specifically with individual impurity levels of not more than about 0.10% for Impurity A, Impurity C, Impurity D, Impurity E, or Impurity F, and not more than about 2.0% for Impurity B.

In one embodiment, the percent total impurities in the composition is determined in an HPLC assay as described in Colchicine Official Monograph USP30/NF25 as 100% times a sum of responses of any peaks other than that due to colchicine, eluting within 1.5 times the retention time for colchicine, relative to a sum of responses of all peaks eluting within 1.5 times the retention time for colchicine and the percent of an individual impurity in the composition is determined in an HPLC assay as described in Colchicine Official Monograph USP30/NF25 as 100% times the responses of the impurity peak relative to a sum of responses of all peaks eluting within 1.5 times the retention time for colchicine.

In yet another embodiment, the percent total and/or individual impurities in the composition is determined in an HPLC assay or UPLC assay in accordance with the methods described in Table 2 or Table 3A or 3C.

In one embodiment, any of the colchicine compositions described above is in the form of a tablet. As used herein, the term "tablet" means a compressed pharmaceutical dosage form of any shape or size. The tablets described herein may be obtained from the compositions comprising colchicine and a pharmaceutically acceptable excipient. Any of the colchicine compositions can be in the form of any other dosage form known in the art, specifically, any oral dosage form, for example a capsule.

Either wet or dry granulation of a colchicine composition may be used prior to compressing the composition into tablets, or direct compression can be used.

In one embodiment, wet granulation is used to prepare wet granules comprising colchicine. A granulating liquid is used in wet granulation process. Both aqueous and non-aqueous liquids may be used as the granulating liquid. In one embodiment, the granulating liquid is an aqueous liquid, or more specifically, de-ionized water. In an embodiment, the colchicine is ultrapure colchicine.

The amount of the granulating liquid used may depend on many factors, for example, the type of the granulating liquid, the amount of the granulating liquid used, whether a hygroscopic excipient is used, the nature of the active agent, and the active agent loading. In one embodiment, the amount of the granulating liquid is in the range of about 5 wt % to about 50 wt %, or more specifically, about 10 wt % to about 40 wt %, based on the dry weight of the granulating particles prior to wet granulation.

Wet granulation time is generally about 5 to 60 minutes. In one embodiment, the colchicine particles and suitable excipients are mixed with the granulating liquid for a period of about 5 to about 45 minutes, or more specifically, about 5 to about 35 minutes. For a small scale, the mixing time is about 1 to about 20 minutes, or more specifically, 3 to 10 minutes. Wet granulation is generally performed at temperatures between about 20° C. to about 35° C., or more specifically, at room temperature (about 25° C.).

Any equipment may be used to contact the granulating liquid with the colchicine and the excipients as long as uniform distribution of the granulating liquid is achieved. For example, small-scale production can be achieved by mixing and wetting the ultrapure colchicine and the excipients in mortars or stainless steel bowls, while for larger quantities, V-blenders with intensifier bars, planetary mixers, rotary granulators, high shear granulators, and fluid-bed granulation equipment may be used. In one embodiment, the granulator is a high shear granulator.

In one embodiment, a method of making a colchicine composition comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a second excipient to obtain a colchicine composition. In one embodiment, the pharmaceutically acceptable excipient comprises a mixture of a filler and a binder. In another embodiment, the mixture of the filler and the binder comprises pregelatinized starch, lactose monohydrate, and microcrystalline cellulose. In another embodiment, de-ionized water is used as the granulating liquid. In some embodiments, the colchicine is ultrapure colchicine. In an embodiment, the second excipient mixed with the granules is a disintegrant. The colchicine compositions can contain about 0.1 wt % to about 10 wt %, or more specifically, about 0.1 wt % to about 1 wt %, of colchicine, based on the total weight of the colchicine composition.

In an embodiment, the method of making a composition comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules, and mixing the granules with a disintegrant to obtain a colchicine composition. In some embodiments, the method further comprises drying the mixture. In another embodiment, the wet granules are dried to obtain dried granules; and then the dried granules are mixed with a disintegrant to obtain the composition. In another embodiment, the dried granules can be milled to obtain milled granules before mixing the milled dried granules with the disintegrant. In one embodiment, greater than 50% of the milled granules pass through a 45 micron sieve or mesh screen. The method can further comprise mixing the colchicine composition with a lubricant to obtain a tableting blend or compressing the tableting blend to obtain a tablet. The method can further comprise coating the tablet.

In one embodiment, a method of making a colchicine composition comprises wet granulating ultrapure colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; and mixing the milled granules with a disintegrant to obtain the composition. The ultrapure colchicine can comprise no more than about 3.0% total impurities, with no more than about 0.10% Impurity A, no more than about 0.15% Impurity F, and no more than about 2.0% Impurity B.

In another embodiment, a method of making a colchicine tablet comprises wet granulating colchicine with a pharmaceutically acceptable excipient to obtain wet granules; drying the wet granules to obtain dried granules; milling the dried granules to obtain milled granules; mixing the milled granules with a disintegrant to obtain the composition; mixing the composition with a lubricant to obtain a tableting blend; and compressing the tableting blend to obtain a colchicine tablet.

In some embodiments, the wet granules are dried to obtain dried granules before mixing with a second excipient, for example a disintegrant. Wet granules can be dried by any suitable means to remove the granulating liquid and to form dried granules containing colchicine and the pharmaceutically acceptable excipient. The conditions and duration of drying depend on factors such as the liquid used and the weight of the granulating particles. Examples of suitable drying methods include, but are not limited to, tray drying, forced air drying, microwave drying, vacuum drying and fluid bed drying.

The extent of drying may be determined by visual observation and manual manipulation, as is common in the art. The extent of drying may also be determined by sieve analysis, moisture measurements, such as loss on drying (LOD) or other suitable methods. In one embodiment, wet granules are dried until the granules lose less than 5 weight percent (wt %), or more specifically, 3 wt % upon drying at 105° C. based on the total weight of the dried granules prior to drying (or LOD of less than 3 wt %).

After drying, dried granules may be mixed directly with an excipient, for example, a filler, a binder, a disintegrant, or a lubricant, for further processing. Alternatively, dried granules may optionally be subjected to additional processing steps prior to mixing with the excipient. For example, dried granules may be sized to reduce particle size prior to mixing with an excipient. Exemplary sizing operations include milling or sieving. Any suitable equipment for reducing the particle size may be used in the present invention. In one embodiment, the dried granules are milled to obtain milled granules so that at least 50% of the milled granules pass through a 45 micron mesh screen.

Suitable excipients may be added extragranularly and mixed with the granules to form colchicine compositions. As used herein, the term "extragranular" or "extragranularly" means that the referenced material, for example, a suitable excipient, is added or has been added as a dry component after wet granulation. In one embodiment, a disintegrant and a lubricant, in that sequence, are added extragranularly to the granules and mixed to form a blend. The blend may be encapsulated directly into capsule shells, for example, hard gelatin shells, to form capsule formulations. Alternatively, the blend may be compressed into tablets. In some embodiments, the granules are dried granules or milled, dried granules. In some embodiments, the colchicine is ultrapure colchicine.

Mixing can be carried out for a sufficient time to produce homogeneous mixtures or blends. Mixing may be accomplished by blending, stirring, shaking, tumbling, rolling, or by any other method to achieve a homogeneous blend. In some embodiments, the components to be mixed are combined under low shear conditions in a suitable apparatus, such as a V-blender, tote blender, double cone blender or any other apparatus capable of functioning under low shear conditions.

The homogenous mixtures or blends are then compressed using any method suitable in the industry.

The colchicine tablets prepared from the above described methods exhibit acceptable physical characteristics including good friability and hardness. The colchicine tablets disclosed herein have friability in the range of about 0% to 3%, specifically about 0 to 1%, more specifically 0% to 0.5%.

The colchicine tablet can be coated. Coating the tablet may be performed by any known process. A coating for the colchicine tablet disclosed herein can be any suitable coating, such as, for example, a functional or a non-functional coating, or multiple functional or non-functional coatings. By "functional coating" is meant to include a coating that modifies the release properties of the total formulation, for example, a sustained-release coating. By "non-functional coating" is meant to include a coating that is not a functional coating, for example, a cosmetic coating. A non-functional coating can have some impact on the release of the active agent due to the initial dissolution, hydration, perforation of the coating, etc., but would not be considered to be a significant deviation from the non-coated composition.

In one embodiment, the tablet is coated with a non-functional coating. The coating can be a white or colored OPADRY® or OPADRY® II (both available from Colorcon, West Point, Pa.), optionally with additional ingredients such as carnauba wax, plasticizers, opacifiers, colorants, and antioxidants. In one embodiment, the coating comprises OPADRY® II and carnauba wax.

In an embodiment, a colchicine composition comprises about 0.6 mgA colchicine; about 12 to about 16 mg pregela-

tinized starch; about 20 to about 24 mg microcrystalline cellulose; about 3.9 to about 4.7 mg sodium starch glycolate; about 0.5 to about 0.7 mg magnesium stearate; and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg. In some embodiments the colchicine composition comprises about 0.6 mgA colchicine, about 14 mg pregelatinized starch, about 22 mg microcrystalline cellulose, about 4.3 mg sodium starch glycolate, about 0.6 mg magnesium stearate, and an amount of lactose monohydrate such that the colchicine dosage form has a total weight of about 100 mg. The colchicine composition can be in the form of a tablet. In some embodiments the tableted composition further comprises a coating comprising Opadry® II and carnauba wax. In an embodiment, the colchicine is ultrapure colchicine.

In one embodiment, a colchicine composition comprising ultrapure colchicine is formulated into an immediate-release formulation. By "immediate-release" is meant a conventional or non-modified release in which greater than or equal to about 75% of the active agent is released within two hours of administration, specifically within one hour of administration.

Active agent release from a pharmaceutical formulation can be analyzed in various ways. One exemplary test is in vitro dissolution. A dissolution profile is a plot of the cumulative amount of active agent released from a formulation as a function of time. A dissolution profile can be measured utilizing the Drug Release Test <724>, which incorporates standard test USP 26 (Test <711>). A profile is characterized by the test conditions selected such as, for example, apparatus type, shaft speed, temperature, volume, and pH of the dissolution medium. More than one dissolution profile may be measured. For example, a first dissolution profile can be measured at a pH level approximating that of the stomach, and a second dissolution profile can be measured at a pH level approximating that of one point in the intestine or several pH levels approximating multiple points in the intestine.

In one embodiment, the immediate-release colchicine composition exhibits a dissolution profile such that at ten minutes after combining the composition with 500 ml of purified water at 37° C.±0.5° C. according to USP 28<711> Apparatus 1 (basket), 100 rpm speed, about 90 to about 100 wt. % of the total amount of active agent is released; specifically at 30 minutes after combining the composition with the dissolution medium, about 95 to about 100 wt. % of the total amount of colchicine is released; and more specifically at one hour after combining the composition with the dissolution medium, about 98 to about 100 wt. % of the total amount of colchicine is released.

Potency, or the amount of active colchicine present in a batch of colchicine, can be determined as described in Colchicine Official Monograph USP 30/NF 25 by comparing an assay sample to a colchicine reference standard (e.g., USP Colchicine RS) sample in the chromatographic assay described in Colchicine Official Monograph USP30/NF25. The quantity of active colchicine in the assay sample, in mg, of $C_{22}H_{25}NO_6$ is calculated by the formula: $10C(r_U/r_S)$, in which C is the concentration, in µg per mL, of the colchicine reference standard sample; and r_U and r_S are the colchicine peak responses obtained from the assay sample and the colchicine reference standard sample, respectively.

In another embodiment, potency of a batch of colchicine can be determined using the HPLC Potency assay described in the table below by comparing an assay sample to a colchicine reference standard.

HPLC Potency Assay B	
Mobile phase	50 mM Potassium Phosphate Buffer:methanol (45:55), pH 5.5 ± 0.05
Column	Phenomenex Luna C8(2), 4.6 mm × 25 cm, 5 µm
Flow rate	1.0 mL/min
Column Temperature	Ambient
Detection	254 nm
Injection volume	20 uL
Sample Conc.	0.120 mg/ml
Run time	15 min

The quantity, in percentage, of $C_{22}H_{25}NO_6$ (active colchicine), on an anhydrous, solvent free basis, in the colchicine assay sample is calculated by the formula:

$$\%\ \text{Purity} = \frac{r_u}{r_s} \times \frac{W_s\ (\text{mg}) \times P \times \left(\frac{100 - M_s - S_s}{100}\right)}{500\ \text{ml}} \times \frac{PV\ (\text{ml})}{VF\ (\text{ml})} \times \frac{VF_1\ (\text{ml})}{SW\ (\text{mg}) \times \left(\frac{100 - M_u - S_u}{100}\right)} \times \frac{VF_2\ (\text{ml})}{PV_1\ (\text{ml})} \times 100$$

Where:

r_u=The peak area of colchicine in the working sample solution

r_s=The peak area of colchicine in the working standard solution

W_s=The weight of colchicine in the standard preparation

P=Standard purity factor expressed as labeled % Purity

M_S=Moisture factor in standard expressed as % Moisture

S_S=Solvent factor in standard expressed as % Solvent

PV=Pipet volume used for the working standard solution

VF=Volumetric flask used for the working standard solution

SW=Sample weight in the stock sample solution

VF_1=Volumetric flask used for the stock sample solution

M_u=Moisture factor in sample expressed as % Moisture

S_u=Solvent factor in sample expressed as % Solvent

VF_2=Volumetric flask used for the working sample solution

PV_1=Pipet volume used for the working sample solution.

Alternatively, potency of a batch of colchicine can be determined by comparing an assay sample to a colchicine reference standard in yet another HPLC assay as follows:

HPLC Potency Assay C	
HPLC System:	HPLC equipped with a pump, autosampler, variable wavelength detector and a suitable data acquisition system
Column Information:	Phenomenex Gemini C18 150 × 4.6 mm 5 µm 110Å
Detection:	245 nm
Flow Rate:	1.5 mL/minute
Injection Volume:	20 µL
Column Temperature:	30° C. ± 3° C.
Needle Rinse Setting:	Double
Sampling Rate:	2.0
Resolution:	1.2
Filter Response:	1.0
Digital Filter:	Enabled

-continued

HPLC Potency Assay C	
Needle Wash/Seal Wash:	Methanol:Water (50:50)
Run Time:	About 15 minutes
Mobile Phase:	pH 6.0 Buffer Solution (50 mM of Potassium phosphate and 4 mM of EDTA):Methanol (60:40)
Diluent:	Water:Methanol (75:25)

The percent purity of Colchicine ($C_{22}H_{25}NO_6$), on an anhydrous, solvent-free basis, is calculated as follows:

$$\% \text{ Assay} = \frac{r_u}{r_s} \times \frac{W_s \text{ (mg)} \times P}{50 \text{ mL}} \times \left(\frac{100 - \%RS_s - \%W_S}{100}\right) \times \frac{5.0 \text{ mL}}{100 \text{ mL}} \times \frac{500 \text{ mL}}{W_u \text{ (mg)} \times \left(\frac{100 - \%RS_u - \%W_u}{100}\right)} \times 100\%$$

Where:

r_u=The peak area response of Colchicine in the Sample Solution.

r_s=The peak area response of Colchicine in the Working Standard Solution.

W_s=The weight of Colchicine in the Stock Standard Preparation.

W_u=The weight of Colchicine in the Sample Preparation.

P=Standard purity factor expressed as labeled (% Purity/100).

% $RS_{s/u}$=Percent of Residual Solvents in the Colchicine Standard/Sample.

% $W_{s/u}$=% Water in the Colchicine Standard/Sample.

Disclosed herein are also methods of treatment and dosing regimens.

The compositions comprising ultrapure colchicine disclosed herein may be used to treat or prevent a patient's condition such as acute gouty arthritis, chronic gouty arthritis, acute pericarditis, asthma, Behçet's disease, cancer, chronic gout (prophylaxis), pseudogout cystic disease comprising polycystic kidney disease or cystic fibrosis, demyelinating disease of central or peripheral origin, Dupuytren's contracture, Familial Mediterranean fever, glaucoma, idiopathic pulmonary fibrosis, idiopathic thrombocytopenic purpura, inflammatory disorder comprising rheumatoid arthritis, lentiviral infection, multiple sclerosis, postpericardiotomy syndrome, primary amyloidosis, primary biliary cirrhosis, proliferative vitreoretinopathy, pyoderma gangrenosum, recurrent pericarditis, or a condition in need of enhanced bone formation or bone mineral density.

The traditional dose of colchicine used to treat or prevent an attack of acute gouty arthritis has been about 1.0 to about 1.2 mgA of colchicine, for example, two tablets each comprising about 0.6 mgA colchicine. This dose may be followed by one unit of the composition every hour, or two units every two hours, until pain is relieved or until diarrhea ensues ("diarrheal dose"). After the initial dose, it is sometimes sufficient to take about 0.6 mgA colchicine every two or three hours. The dosing should be stopped if there is gastrointestinal discomfort or diarrhea. (Opiates may be needed to control diarrhea.) In subsequent attacks, the patient should be able to judge his medication requirement accurately enough to stop short of his diarrheal dose. The total amount of colchicine needed to control pain and inflammation during an attack has been believed to be in the range from about 4 mgA to about 8 mgA. An interval of three days between colchicine courses is advised in order to minimize the possibility of cumulative toxicity.

In one embodiment, a method of treating acute gouty arthritis comprises administering two colchicine dosage forms each comprising about 0.6 mgA colchicine at the onset of the acute gout attack, followed by one dosage form every hour for m hours, wherein the value of m is 1 to 8. In one embodiment, the value of m is 1 to 6. In another embodiment, the value of m is 1 (total of 3 tablets). In yet another embodiment, the value of m is 6 (total of 8 tablets). The colchicine in the dosage form can be ultrapure colchicine. The dosage form can be any oral dosage form, specifically a tablet.

In another embodiment, a method of treating Familial Mediterranean Fever comprises administering ½ dosage form to four dosage forms daily, each dosage form comprising about 0.6 mgA colchicine (total of about 0.3 to about 2.4 mgA colchicine daily). In another embodiment, a method of prophylactically treating chronic gout comprises administering one-half dosage form, one dosage form, two dosage forms, or three dosage forms, each dosage form comprising about 0.6 mgA of colchicine, daily. In another embodiment, a method of treating Behçet's disease comprises administering one dosage form comprising about 0.6 mgA of colchicine twice daily (total of 2 dosage forms). The colchicine in the dosage form can be ultrapure colchicine. The dosage form can be any oral dosage form, specifically a tablet.

In one embodiment, a method of treating patients with some but not all of the symptoms of acute gout, chronic gout (prophylaxis), or pseudogout, where the patients are not clinically or informally diagnosed with one of these diseases, comprises administering one or more of the dosage forms comprising about 0.6 mgA of colchicine. The colchicine in the dosage form can be ultrapure colchicine.

The invention should not be considered limited to these particular conditions for combining the components and it will be understood, based on this disclosure that the advantageous properties can be achieved through other conditions provided the components retain their basic properties and substantial homogeneity of the blended formulation components of the formulation is otherwise achieved without any significant segregation.

The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Exemplary Ultrapure Colchicine

As discussed above, ultrapure colchicine with reduced levels of individual and total impurities was desired by the inventors for formulation into a new dosage form in order to minimize potential adverse reactions from the impurities in patients taking the dosage form and to reduce the expense of qualification testing during the approval process for marketing the new dosage form. Batches of conventional colchicine were previously obtained from Sanmar Specialty Chemicals Limited (Berigari, India). Conventional colchicine can be further purified to form ultrapure colchicine meeting the following impurity specifications:

TABLE 4

Purity Specifications for an exemplary batch of Ultrapure Colchicine

Impurity, Common name	Impurity	NMT %
N-deacetyl-N-formyl colchicine	A	0.10
Conformational isomer	B	1.0

TABLE 4-continued

Purity Specifications for an exemplary batch of Ultrapure Colchicine

Impurity, Common name	Impurity	NMT %
β-Lumicolchicine	C	0.10
Colchicoside	D	0.10
3-O-demethyl colchicine	E	0.10
Total Impurities		2.0

Ultrapure colchicine was prepared to meet the purity specifications in Table 4 as described below.

First, conventional colchicine was obtained from a colchicine chloroform extract. The extract was washed with a mixture of purified water, sodium hydroxide solution, sodium chloride solution and acetic acid. The washed extract was filtered and the resulting concentrate was distilled in two steps, first using methanol, and second using ethyl acetate. The resulting distillate was crystallized. Ethyl acetate was used to isolate and wash the crystallized colchicine, which was then dried, resulting in the conventional colchicine. This process is also referred to herein as the "old process".

Second, the conventional colchicine was then subjected to column chromatography on neutral alumina using methylene chloride as solvent. The resulting concentrate was distilled using ethyl acetate, crystallized, isolated and washed using ethyl acetate, and dried, resulting in ultrapure colchicine. This method of generating conventional colchicine, followed by the additional chromatography purification step is also referred to herein as the "new process".

The impurity levels of the lot of ultrapure colchicine and two lots of conventional colchicine were analyzed using the USP30/NF25 Colchicine Official Monograph HPLC method ("USP method") described in Table 2 above. The impurity levels are shown in Table 5.

TABLE 5

	Impurity Level, %			
Colchicine Lot	N-Deacetyl-N-formyl colchicine - Impurity A	Conformational Isomer - Impurity B	Total Unidentified Impurities	Total Impurities
Ultrapure (RD0600164)	ND*	0.5	ND*	0.5
Conventional-1 (RD060075)	2.1	0.6	ND*	2.7
Conventional 2 (RD060055)	2.2	0.6	ND*	2.8

*ND—None detected.

Table 5 shows that ultrapure colchicine has fewer impurities than each of the conventional colchicine lots. Total impurities of the Ultrapure Lot using the USP method were about 0.5%. On the other hand, total impurities of conventional Lots #1 and 2 were about 2.7% and 2.6%, respectively.

Determined impurity levels may differ depending on the test method used. Table 5B contrasts the determined levels of the conformational isomer, Impurity A (N-deacetyl-N-formyl colchicine), and total impurities for the three colchicine lots using the three methods described in Table 2. The three methods show a maximum absolute variability in the percent determined of 0.8% for N-deacetyl-N-formyl colchicine, of 0.5% for conformational isomer, and 0.7% for total impurities.

TABLE 5B

Levels of impurities in colchicine lots determined using methods of Table 2.

		Conformational Isomer			N-deacetyl-N-formyl colchicine			Total Impurities		
Lot name (Lot #)	Purification Process	UPLC Method	HPLC Method	USP Method	UPLC Method	HPLC Method	USP Method	UPLC Method	HPLC Method	USP Method
Conventional-1 (RD060055)	Old	0.9	0.8	0.6	3.0	2.5	2.2		3.5	2.8
Conventional 2 (RD060075)	Old	0.9	0.8	0.6	2.7	2.3	2.1		3.2	2.7
Ultrapure (RD0600164)	New	0.9	1.0	0.5	ND*	ND	ND		1.1	0.5

*ND, none detected.

Regardless of the testing method used for measuring these impurity levels, the impurity levels for ultrapure colchicine manufactured using the new process remains below the specifications set forth in Table 4.

The ultrapure colchicine of the present invention was prepared to meet the organic volatile impurity specifications ("residual solvents") in Table 6 as described below. The residual solvents are determined using USP <467> test method. In addition to the known and existing solvents, specifications were also set for residual solvent peaks that were seen in HPLC assay testing as described in Tables 2, 3A, or 3C, which solvents are not expected or previously existing for the residual solvent test methods for colchicine or were not identifiable.

TABLE 6

Specifications for Organic Volatile Impurities

Organic volatile	NMT
Chloroform	100 ppm
Methanol	3000 ppm
Methylene Chloride	600 ppm
Ethanol	5000 ppm
Ethyl Acetate	6.0%
Ethyl Propionate	5000 ppm
Propyl Acetate	5000 ppm
Others	500 ppm each

Example 2

Stable Tablets Comprising Ultrapure Colchicine

Stable colchicine compositions comprising the ultrapure colchicine described in Example 1 were manufactured using

the following process. Ultrapure colchicine as described in Example 1 was dissolved in purified water. Pregelatinized starch (Starch® 1500), lactose monohydrate, NF (Fast Flo), and microcrystalline cellulose, NF (Avicel PH101) were placed in a 150-liter high shear granulator and mixed. The aqueous ultrapure colchicine solution was added to the granulator while mixing. The wet granules were dried in an oven at 50° C. until the loss on drying of the material was less than 3 wt %. The dried granules were milled through a Fitzmill equipped with a 1A screen.

The milled granules were charged into a 5 cubic foot Gemco Double Cone Blender and blended with screened sodium starch glycolate, NF (GLYCOLYS®). Then, screened magnesium stearate, NF was added to the blender. Blending was continued and a final tableting blend was made. This final tableting blend was compressed into core tablets. These core tablets were film-coated with OPADRY® II purple and carnauba wax. The composition of the ultrapure colchicine tablets is shown in Table 7.

TABLE 7

Ingredient	Amount Per Tablet, mg
Ultrapure Colchicine	0.6[1]
Pregelatinized starch, NF (Starch 1500)	14.0
Lactose Monohydrate, NF (Fast Flo)	Varies[2]
Microcrystalline Cellulose, NF (Avicel PH101)	21.6
Sodium Starch Glycolate, NF (GLYCOLYS)	4.3
Magnesium Stearate, NF	0.6
Total core tablet	100
OPADRY II Purple (#40L10039)	4.0
Carnauba Wax	0.01

[1]Colchicine amount is shown in units of mgA, adjusted for purity of the lot of colchicine.

[2]Amount adjusted, depending on the actual amount of the colchicine lot added, to maintain an overall core tablet weight of 100 mg.

As a comparison, the lot of conventional colchicine designated in Example 1 as "conventional-2" was substituted in place of ultrapure colchicine in the same tablet formulation shown in Table 7. The same process of making the tablets as described above was used.

The impurities in the tablet comprising the ultrapure colchicine and that comprising the conventional colchicine were analyzed using the HPLC method described in Table 2 above. The impurity levels of both colchicine tablets are shown in Table 8.

TABLE 8

			Impurity Content, %			
Colchicine Product Lot	Colchicine Lot	Process	N-Deacetyl-N-formyl colchicine (Impurity A)	Conformation Isomer (Impurity B)	Total Unknown Impurities	Total Impurities
A	Ultrapure	New	ND*	1.1	0.1	1.2
B	Conventional-2	Old	2.3	1.2	ND*	3.6

*ND—None detected.

It can be seen from Table 8 that the tablet comprising the ultrapure colchicine has less total impurities than that comprising the conventional colchicine.

The colchicine composition comprising ultrapure colchicine at 6 month stability time points under conditions of 25° C./60% relative humidity and 40° C./60% relative humidity exhibits impurity content ranges of Not Detected to about 0.1% for Impurity A, less than about 1.0% for total unknown impurities compared to a colchicine composition comprising conventional colchicine which exhibits impurity content of greater than about 1.5 for Impurity A and greater than about 2.0% for total unknown impurities when tested under the same conditions.

Table 9 below provides data on impurity levels and stability of impurity levels of colchicine composition batches manufactured using ultrapure and conventional colchicine, and impurity levels for two lots of commercially available COL-PROBENECID® tablets (Watson Laboratories), an FDA-approved combination dosage form comprising colchicine and probenecid.

TABLE 9

		Colchicine	Conditions	Conformational Isomer		N-Deacetyl peak	
Material	Lot	purification Process	of Stability Study	UPLC Method	HPLC Method	UPLC Method	HPLC Method
COL-PROBENECID ® (Probenecid/ Colchicine) Tablets†	L6C0395	N/A	N/A	0.8	—	2.2	—
	L6M1440	N/A	N/A	0.8	—	2.5	—

TABLE 9-continued

Material	Lot	Colchicine purification Process	Conditions of Stability Study	Conformational Isomer UPLC Method	Conformational Isomer HPLC Method	N-Deacetyl peak UPLC Method	N-Deacetyl peak HPLC Method
Colchicine Product Lot	B	Old process	room temp, at release	0.9	1.2	2.8	2.3
			12 mo 25 C./60% RH	0.9	0.9	2.7	2.6
	A	New process	room temp, at release	1.0	1.2	ND	ND
			6 mo 25 C./60% RH	1.0	0.8	ND	ND
			6 mo 40 C./75% RH	1.0	1.1	ND	ND
	C	New process	room temp, at release	1.0	1.1	ND	ND
			6 mo 25 C./60% RH	0.9	0.9	ND	ND
			6 mo 40 C./75% RH	1.0	1.1	ND	ND
	D	New process	room temp, at release	1.0	1.1	ND	ND
			6 mo 25 C./60% RH	1.0	1.0	ND	ND
			6 mo 40 C./75% RH	0.9	1.1	ND	ND

—, not analyzed;
†Commercially avaiable;
N/A, not applicable;
ND, none detected.

For comparison, several lots of an FDA-approved colchicine-probenecid combination dosage form and various unapproved commercial colchicine dosage forms were tested for levels of impurities using the HPLC method of Table 2. Results are shown in the tables below.

Impurities in FDA-Approved Colchicine/Probenecid Combination Product

Impurity	Watson Laboratories Colchicine/Probenecid Tablets L7G1085	L7G1085	L7G1087	L7E0808
Conformational Isomer	1.0%	1.0%	0.8%	1.0%

-continued

Impurities in FDA-Approved Colchicine/Probenecid Combination Product

Impurity	Watson Laboratories Colchicine/Probenecid Tablets L7G1085	L7G1085	L7G1087	L7E0808
N-deacetyl-N-formyl colchicine	2.0%	2.0%	1.5%	2.0%
Largest Unknown	0.1%	0.1%	0.1%	0.1%
Total Impurities	3.1%	3.1%	2.4%	3.2%

Impurities in Unapproved Colchicine Products

Impurity	West-Ward 62303A*	63842A	63843A	Vision C07003	C07049	C07058
Exp Date	Jan-2009	May-2011	May-2011	Jan-2009	Aug-2009	Sep-2009
Conformational Isomer	1.1/0.9%	0.9%	0.9%	1.1/0.8%	0.9%	0.9%
N-deacetyl-N-formyl colchicine	2.5/2.6%	2.0%	1.8%	1.3/1.3%	2.7%	2.6%
Largest Unknown	1.7/1.6%	0.5%	0.3%	0.1/0.1%	0.1%	0.3%
Total Impurities	5.3/5.3%	3.5%	3.1%	2.5/2.3%	3.8%	4.0%

Impurity	Qualitest T105G07A	T107G07A	T108G07A	Akyma 3A5246004*
Exp Date	Jul-2010	Jul-2010	Aug-2010	Jan-2008
Conformational Isomer	1.0%	0.9%	0.9%	1.1/0.9%
N-deacetyl-N-formyl colchicine	%1.4	1.3%	1.3%	1.4/1.5%
Largest Unknown	0.3%	0.2%	0.2%	0.2/0.1%
Total Impurities	2.7%	2.7%	2.6%	2.9/2.5%

*Values from two separate analyses reported

Summary of Impurities in Marketed Colchicine Products with Batches of colchicine tablets using ultrapure colchicine

	Marketed Colchicine Products		Product Lots with Ultrapure Colchicine
Impurity	Minimum	Maximum	Maximum
Conformational Isomer	0.8%	1.1%	1.1%
N-deacetyl-N-formyl colchicine	1.3%	2.7%	ND
Largest Unknown	0.1%	1.7%	0.3%
Total Impurities	2.4%	5.3%	1.4%

ND = none detected

The total impurities found in ultrapure colchicine and colchicine products comprising ultrapure colchicine are significantly lower compared to the approved and unapproved, marketed colchicine products. In addition, the maximum total impurities value observed by testing 14 approved or unapproved marketed products was 5.3%; while the maximum value seen to date in inventive ultrapure colchicine product batches was 1.4%. This represents a 75% reduction in total impurities.

Of particular significance, the level of the known impurity, N-deacetyl-N-formyl-colchicine (Impurity A, also known as Gloriosine) has been reduced from levels exceeding 2% to undetectable levels that comply with the ICH Q3A(R2) qualification threshold of 0.15% for an active agent. Gloriosine is tumorigenic and has been studied as an anti-cancer agent. Purification of conventional colchicine to obtain ultrapure colchicine has effectively reduced all individual impurity levels in the colchicine to substantially reduce exposure of patients to this tumorigenic impurity.

Example 3

Therapeutic Effects of Ultrapure Colchicine Formulation

The therapeutic effect of the ultrapure colchicine formulation containing 0.6 mgA of colchicine obtained in Example 2 is evaluated in a clinical study that is a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1-week, dose comparison study designed to evaluate the efficacy of ultrapure colchicine in treating an acute gout attack (acute gouty arthritic attack) in patients with acute gout. A sufficient number of patients are screened to enroll and randomize 300 patients (100 patients per treatment group) who meet the criteria of the American College of Rheumatology (ACR) for acute arthritis of gout. The primary objective of the study is to demonstrate the efficacy of colchicine in an acute gout attack (gouty flare) based on pain reduction after 24 hours as a measure of response. Secondary objectives of the study are to compare low-dose and standard-dose dosing regimens of colchicine with respect to pain, time to response and complete pain relief, interference with sleep, and signs and symptoms of inflammation and to determine the safety of colchicine when administered in the two different dosing regimens.

Description of Study

The study will consist of three distinct phases and the number of visits to the study clinic will vary depending on conditions pertaining to an individual patient's acute gout flare experienced in the study as described below. The Pre-Flare Phase will consist of up to two visits to the study clinic (with additional interim visits for clinical laboratory testing every 3 months until acute gout flare onset): Visit 1 (Screening) and Visit 2 (Randomization). The Flare Phase will not include a visit to the study clinic. The Post-Flare Phase will consist of up to three visits to the study clinic: Visit 3 (as soon as possible [ASAP] up to 48 hours post-flare onset; if a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be waived and the patient should return to the clinic for Visit 4), Visit 4 (>48 to 96 hours post-flare onset in patients who took at least one dose of study drug and in patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3), and Visit 5 (7 days post-flare onset to be conducted in patients who took at least one dose of study drug and whose acute gout flare was still ongoing at Visit 4). For those patients in whom the acute gout flare is not resolved at Visit 5 (based on the judgment of the Investigator) or in whom there is an unresolved AE or clinically significant treatment-emergent laboratory abnormality, there will be one additional follow-up visit 14 days post-flare onset (Visit 6).

When a patient develops an acute gout flare, the patient will call the trained personnel at the Gout Flare Call Center (available 24 hours/day throughout the duration of the study). The patient will be queried regarding any changes in his/her medical health and concomitant medication use since the time of randomization. In order to establish if the patient's acute gout flare will be eligible for treatment with study drug, a standardized questionnaire will be used to document that the patient has all of the following signs/symptoms of the affected joint(s): swelling, erythema, marked tenderness, and pain. In addition, a patient must have at least one of the following: rapid onset of maximum pain within the prior 4 to 12 hours, decreased range of motion in the joint, warmth, or other symptom similar to a prior gout flare. Patients will be asked to rate the pain severity for each joint affected by the acute gout flare by using a study diary. Patients must have at least one joint affected by an acute gout flare with a pain assessment of ≧4 on the PI-NRS at the onset of the acute gout flare during the Flare Phase prior to taking study drug. If signs and symptoms of an acute gout flare are confirmed and the gout flare is considered eligible for treatment with study drug, the patient will also be instructed to begin taking study drug and to continue completing the patient diary. Patients will be instructed to stop taking study drug and to call the investigational site if at any time they experience a severe gastrointestinal event while taking study drug. The Gout Flare Call Center will call the patient in 24 hours from the onset of the acute gout flare to ensure that the patient has completed the patient diary, including assessments for pain at 24 hours.

In the event that the Gout Flare Call Center determines that the patient does not qualify for treatment with study drug, the patient may be asked to call back in 1 hour for re-assessment. Patients who do not qualify for treatment with study drug may seek alternative therapy without prejudice to further study participation should another acute gout flare occur.

The Gout Flare Call Center will contact patients on a monthly basis beginning 1 month after randomization to study drug. These contacts will continue until the patient has an acute gout flare or study completion, whichever occurs first. The purpose of these contacts is to re-educate patients about study participation.

Post-Flare Phase:

Visit 3: After developing an acute gout flare, whether eligible for treatment with study drug or not, all patients will return to the clinic as soon as possible after acute gout flare onset for clinical assessments. If a patient cannot complete Visit 3 in the first 48 hours post-flare onset, Visit 3 will be

waived and the patient should return to the clinic for Visit 4. For patients whose acute gout flare was deemed eligible for treatment with study drug and at least one dose of study drug was taken, Investigators will examine the patient and complete clinical assessments, patient diaries will be collected, the patient will be queried for concomitant medication use and Adverse Events (AEs), and the study drug blister pack will be collected. For patients whose acute gout flare was deemed not eligible for treatment with study drug by the Gout Flare Call Center, continued eligibility for the study will be confirmed by the Investigator based on review of the inclusion and exclusion criteria as well as the responses to the standardized questionnaire and examination of the patient. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs.

Visit 4: The second Post-Flare Phase visit is to be conducted >48 to 96 hours following acute gout flare onset. It will take place in patients who took at least one dose of study drug and also in those patients who did not qualify for treatment with study drug during the Flare Phase but did not complete Visit 3. For patients whose acute gout flare was deemed eligible for treatment with study drug and at least one dose of study drug was taken, Investigators will examine the patient and complete clinical assessments, patient diaries will be collected, patients will be queried for concomitant medication use and AEs, and the study drug blister pack will be collected (if not previously collected). Patients who took at least one dose of study drug and whose acute gout flare is still ongoing at Visit 4 will return to the clinic for a final visit (Visit 5) 7 days post-flare onset; however, if their acute gout flare is resolved at Visit 4, final study assessments, including collection of samples for laboratory safety and a complete physical examination, will be performed at Visit 4. For patients whose acute gout flare was deemed not eligible for treatment with study drug by the Gout Flare Call Center who did not have a Visit 3, continued eligibility for the study will be confirmed by the Investigator based on review of the inclusion and exclusion criteria as well as the responses to the standardized questionnaire and examination of the patient. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs.

Visit 5/Early Termination: The final visit for the study will take place 7 days after the acute gout flare onset in patients who took at least one dose of study drug and whose acute gout flare was still ongoing at Visit 4. Patients will be examined and clinical assessments will be made. A complete physical examination will be conducted. Samples for clinical laboratory testing will be collected. Patient diaries will be collected and patients will be queried for concomitant medication use and AEs. The study drug blister pack will be collected (if not previously collected).

Visit 6/Follow-up: For those patients in whom the acute gout flare is not resolved at Visit 5 (based on the judgment of the Investigator) or in whom there is an unresolved AE or clinically significant treatment-emergent laboratory abnormality, there will be one additional follow-up visit 14 days post-flare onset (Visit 6).

For inclusion in the study, a patient must be 18 years of age or older, must present with a confirmed diagnosis of gout consistent with the criteria of the ACR, and must have experienced ≧2 acute gouty arthritic attacks in the 12 months prior to randomization. Patients on urate-lowering therapy must be on a stable dose and schedule with no changes in therapy for 4 weeks prior to randomization and expected to remain on a stable regimen during study participation.

Patients with acute polyarticular gout (>4 joints); taking colchicine routinely; with a known hypersensitivity to colchicine; with a history of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting; with active myeloid leukemia, obstructive gastrointestinal cancer, or metastatic cancer; with chronic renal dysfunction, with chronic hepatic dysfunction are excluded from the study. Patients using systemic corticosteroid, cyclosporine, adalimumab, etanercept, infliximab, anakinra, abatacept, mycophenolate, azathioprine, or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, and other analgesics such as opiates at screening are also excluded.

The three treatment groups in this study are two ultrapure colchicine tablets (1.2 mgA) administered at the onset of an acute gout attack followed by one tablet (0.6 mgA) after one hour and one placebo tablet every hour thereafter for 5 hours (the "low" dose regimen); two ultrapure colchicine tablets (1.2 mgA) administered at the onset of an acute gout attack followed by one tablet (0.6 mgA) every hour for six (6) hours (the "standard" dose regimen); or two placebo tablets at the onset of an acute gout attack followed by one placebo capsule every hour thereafter for 6 hours (the "placebo" regimen).

Efficacy assessment will be made based on patient and Investigator inputs. Patients will record pain severity and sleep interference on a study diary. The severity of pain for each joint affected by the acute gouty arthritic attack will be rated on an 11-point pain intensity numerical rating scale (PI-NRS) that ranges from 0 ("no pain") to 10 ("worst possible pain"). Recordings are to be made prior to each dose of study drug, i.e., pre-treatment with study drug and for the first 8 hours following start of treatment, and every 8 hours thereafter (while awake) until symptoms disappear or 72 hours have passed since the first dose of study drug was taken, whichever occurs first. The patient's pain assessment of each affected joint as reported by the patient at pre-treatment with study drug and at 24 hours post-start of study drug will be documented by a central Study Center to be used in the event the patient fails to provide data on his/her study diary for either of these two key time points. In the morning upon awakening, the patient is to rate sleep interference due to the acute gout flare in the study diary on an 11-point scale that ranges from 0 ("pain did not interfere with sleep") to 10 ("pain completely interfered; patient was unable to sleep"). Investigators will provide clinical assessments in the clinic at all Post-Flare Phase study visits, and at medically necessary intervening visits. For these assessments, each of the patient's joints affected by the acute gouty arthritic attack will be examined and signs and symptoms of inflammation will be rated (erythema [absent, present, or not assessable], swelling [0, "none" to 3, "severe"], and tenderness to touch [0, "none" to 3, "severe"]). At the final clinic visit, the Investigator will also provide a global assessment of response to treatment ranging from 0 ("excellent") to 4 ("none").

The primary efficacy variable is response to treatment in the target joint, based on patient self-assessment of pain at 24 hours post-dose. The target joint is identified during data analysis as that joint affected by the acute gout flare with the highest baseline pain score on the patient diary. Ties among maximum joint scores for an individual are resolved by random selection. A responder is one who provides both a pre-treatment and valid 24-hour pain score and achieves a >50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and does not use rescue medication. Patients who use rescue medication, discontinue prior to the 24-hour post-dose assessment, or do not achieve a >50% reduction in pain score at the 24 hour post-dose assessment relative to the pre-treatment score are deemed non-responders.

The secondary efficacy variables are assessments of magnitude of pain reduction, time to response, time to complete pain relief, and interference with sleep as recorded on patient diaries by the patient. Signs and symptoms of inflammation per Investigator's clinical assessments of the target joint are evaluated. Time to drop out (use of rescue medications) is also evaluated. Investigator global assessment of response to treatment is assessed.

The primary efficacy analysis will be based on an Intent-to-Treat (ITT) population, defined as all patients who were randomized, contacted the Gout Flare Call Center, took at least one dose of study drug, and had one subsequent contact. The Per Protocol (PP) population is defined as the subset of the ITT population confirmed by the Investigator as continuing to meet all major inclusion and exclusion criteria and initiating treatment within 12 hours of the onset of the acute gout flare. Analyses will also be made on an Evaluable patient population with an Evaluable patient defined as one who, in addition to being included in the PP population, completed the randomized treatment course. The ITT population will be used for the evaluation of safety.

Statistical tests for efficacy analysis are two-tailed with an alpha significance level of 0.05.

For primary efficacy analysis, the number of responders in the standard-dose colchicine group and the placebo group, as defined for the primary efficacy variable, will be compared using the Mantel-Haenszel chi-square test stratified on study site. The comparison of the standard-dose colchicine and placebo groups of the ITT population is the primary comparison of interest. The sensitivity to alternate definitions of response (based both on magnitude of reduction from baseline as well as time point) will be evaluated as secondary endpoints. As additional sensitivity analyses, these tests will also be repeated for the PP and Evaluable populations if the sample sizes differ from the overall ITT population by more than 10%.

For secondary efficacy analysis, the number of responders in the low-dose colchicine group will be compared to placebo and also to standard-dose colchicine using the Mantel-Haenszel chi-square test stratified on study site. Change in pain intensity, interference with sleep, time to 50% reduction in pain, and time to complete pain relief will be analyzed as continuous variables using analysis of covariance with study site, treatment group, and site by treatment interaction as independent variables for change in pain intensity and interference with sleep, with baseline score as a covariate. For the Investigator's clinical assessment of inflammation (erythema, swelling, and tenderness to touch) and Investigator's global assessment of response to treatment, the treatment groups will be compared using the Mantel-Haenszel chi-square test stratified on study site.

Safety assessments will be made based on patient and Investigator inputs. Patients will be initially screened in the clinic for inclusion by review of medical history and concomitant medication use, physical examination, measurement of vital signs (oral temperature, sitting radial or brachial pulse rate, respiratory rate, and sitting blood pressure), body weight, and clinical laboratory testing (serum biochemistry, complete blood count, and urinalysis). After randomization, clinical laboratory tests, concomitant medication use, medical history and current complaints (AE) will be reviewed every 3 months until an acute gout flare occurs in order to ensure continued eligibility. Compliance with key inclusion/exclusion criteria (based on intervening medical history and concomitant medication use) will be re confirmed by the Gout Flare Call Center prior to authorizing the start of study drug. Following the start of study drug, patients will record any severe gastrointestinal AEs on their diaries and these will be recorded in the Case Report Form (CRF) at each clinic visit. Full physical examinations and clinical laboratory testing will be conducted at the final clinic visit (Visit 4 or Visit 5). Vital signs and body weight will be measured at each Post Flare visit (Visit 3 and 4 or 5). For those patients in whom there is an unresolved AE or clinically significant treatment emergent laboratory abnormality, there will be one additional follow up visit 14 days post flare onset (Visit 6).

Safety analysis will be performed by coding adverse events using a standardized medical dictionary and the incidence summarized by treatment group; tabulations will be prepared of all AEs as well as by relationship and by severity. Adverse events resulting in termination and events meeting regulatory criteria for seriousness will also be tabulated separately. Descriptive statistics (mean, median, standard deviation, and range) of clinical laboratory testing results and vital sign measurements will be generated for each treatment group and change from the most recent value prior to onset of the acute gout flare calculated; no inferential testing will be performed. Treatment emergent abnormalities on physical examination will be tabulated and listed by treatment group. By patient listings of all safety data and concomitant medication use will be generated.

Study Results

The following data were obtained in general accordance with the above protocol.

Out of 813 patients screened, 575 were randomized to treatment with 185 patients having a gouty flare and receiving study drug. The intent-to-treat population consisted of 184 patients (52 received standard dose, 74 received low dose and 58 received placebo).

Number of Responders Based on Target Joint Pain Score at 24 Hours Post First Dose

Colchicine Dose			Odds Ratio (95% Confidence Intervals)		
Low	High	Placebo			
(N = 74) N (%)	(N = 52) N (%)	(N = 58) N (%)	Low vs. Placebo	High vs. Placebo	High vs. Low
28 (37.8)	17 (32.7)	9 (15.5)	3.31 (1.41, 7.77) P = 0.0046	2.64 (1.06, 6.62) P = 0.0343	0.80 (0.38, 1.68) P = 0.5529

Cumulative Distribution of Degree of Percent Improvement for Target Joint Pain Score at 24 Hours Post First Dose

% Improvement	Colchicine Dose High (N = 52)	Low (N = 74)	Placebo (N = 58)
>=0%	52(100.0%)	74(100.0%)	58(100.0%)
>=10%	32(61.5%)	47(63.5%)	24(41.4%)
>=20%	29(55.8%)	45(60.8%)	21(36.2%)
>=30%	21(40.4%)	39(52.7%)	17(29.3%)
>=40%	21(40.4%)	36(48.6%)	14(24.1%)
>=50%	19(36.5%)	30(40.5%)	10(17.2%)
>=60%	15(28.8%)	24(32.4%)	7(12.1%)
>=70%	10(19.2%)	20(27.0%)	4(6.9%)
>=80%	9(17.3%)	15(20.3%)	3(5.2%)
>=90%	6(11.5%)	9(12.2%)	2(3.4%)
>=100%	6(11.5%)	8(10.8%)	2(3.4%)

Treatment Response Based on at Least a 2-Unit Reduction in Target Joint Pain Score at 24Hours and 32 Hours Post First Dose

	Number (%) of Responders			Treatment Comparisons		
	Colchicine Dose			(Odds Ratio and 95% CI)[1]		
Hours Post First Dose	High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
24	18 (34.6)	32 (43.2)	10 (17.2)	2.54 (1.04, 6.18) p = 0.0368	3.66 (1.61, 8.32) p = 0.0015	0.69 (0.33, 1.45) p = 0.3298
32	20 (38.5)	34 (45.9)	10 (17.2)	3.00 (1.24, 7.24) p = 0.0126	4.08 (1.80, 9.27) p = 0.0005	0.74 (0.36, 1.51) p = 0.4033

[1]The p-value is from the unstratified Pearson chi-square test.

Target Joint Pain at Baseline, 24 Hours and 32 Hours Post First Dose, and Change from Baseline (LOCF)-ITT Population

		Colchicine Dose			Treatment Comparisons[1]		
Time Point	Statistic	High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
24 Hours Post First Dose							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	−1.3	−1.5	0.2
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0145	p = 0.0055	p = 0.7540
Change	Mean (SD)	−2.0 (2.93)	−2.2 (3.46)	−0.7 (2.77)			
	Median (Mix, Max)	−2.0 (−9, 4)	−2.0 (−9, 5)	−0.0 (−8, 4)			
32 Hours Post First Dose							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	−1.6	−1.6	0.1
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0057	p = 0.0038	p = 0.9238
Change	Mean (SD)	−2.3 (3.05)	−2.4 (3.59)	−0.7 (2.95)			
	Median (Mix, Max)	−2.0 (−9, 3)	−2.5 (−9, 5)	0.0 (−8, 4)			

[1]Tabled values are the difference between treatment groups mean change from baseline and p-value from ANCOVA with treatment group as the independent variable and baseline score as the covariate.

Total Pain Relief (TOTPAR) Based on All Target Joint Pain Scores

		Colchicine Dose		
Time Point	Statistic	High (N = 52)	Low (N = 74)	Placebo (N = 58)
Hour 24	n	51[1]	74	58
	Mean (SD)	20.9 (48.42)	30.5 (61.44)	9.5 (45.87)
	Median	11.5	23.0	7.3
	(Mix, Max)	(−102, 135)	(−112, 185)	(−90, 142)
Hour 32	n	51	74	58
	Mean (SD)	31.9 (63.83)	45.5 (82.05)	12.2 (59.88)
	Median	27.5	34.1	7.3
	(Mix, Max)	(−102, 185)	(−128, 257)	(−114, 142)

[1]Patient 1026-1005 did not have a diary and the 24-hour call to the Call Center was 27 hours after the initial call. As indicated in the SAP, the Call Center pain score was not eligible for substitution for the missing diary. This patient has been excluded from the TOTPAR summary.

Number (%) of Patients Using Rescue Medication Up to and Including the 24-Hour Post First Dose Assessment

Colchicine Dose			Treatment Comparison		
High	Low	Placebo	(Odds Ratio and 95% CI)		
(N = 52) n (%)	(N = 74) n (%)	(N = 58) n (%)	High vs. Placebo	Low vs. Placebo	High vs. Low
18 (34.6)	23 (31.1)	29 (50.0%)	0.53 (0.25, 1.14) p = 0.1034	0.45 (0.22, 0.92) p = 0.0273	1.17 (0.55, 2.50) p = 0.6768

Change from Baseline in Target Joint Pain Scores at 24 Hours Post First Dose with Interval of Time of Dose Relative to Flare Onset as Covariate (LOCF)-ITT Population

		Colchicine Dose			Treatment Comparisons[2]		
	Statistic	High (N = 52)	Low (N = 74)	Placebo (N = 58)	High vs. Placebo	Low vs. Placebo	High vs. Low
Early Treatment Start (within 4 hours)							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	−1.3	−1.5	0.2
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0145	p = 0.0055	p = 0.7540
Change	Mean (SD)	−2.0 (2.93)	−2.2 (3.46)	−0.7 (2.77)			
	Median (Mix, Max)	−2.0 (−9, 4)	−2.0 (-9, 5)	−0.0 (−8, 4)			
Late Treatment Start (after 4 hours)							
Baseline	Mean (SD)	6.9 (1.59)	6.9 (1.72)	6.8 (1.44)	−1.6	−1.6	0.1
	Median (Mix, Max)	7.0 (4, 10)	7.0 (4, 10)	7.0 (4, 10)	p = 0.0057	p = 0.0038	p = 0.9238
Change	Mean (SD)	−2.3 (3.05)	−2.4 (3.59)	−0.7 (2.95)			
	Median (Mix, Max)	−2.0 (-9, 3)	−2.5 (−9, 5)	0.0 (−8, 4)			

[1] Patient 1016-1013 was missing a flare onset time and Patients 1002-1007, 1018-1008, 1006- 1013, 1009-1011, 1010-1005, 1010-1010, 1026-1002, 1026-1007, 1064-1007, and 1068-1022 appear to have taken the first dose of study medication prior to flare onset.
[2]Tabled values are the difference between treatment groups mean change from baseline and p-value from ANCOVA with treatment group as the independent variable and baseline score as the covariate.

Overall Summary of Treatment Emergent Adverse Events - Safety Population

	Colchicine Dose		
	High (N = 52) n (%)	Low (N = 74) n (%)	Placebo (N = 59) n (%)
Total Number of TEAEs[1]	85	34	27
Number (%) of Patients with at Least One TEAE	40 (76.9)	27 (36.5)	16 (27.1)
Number (%) of Patients with at Least One Mild TEAE	15 (28.8)	19 (25.7)	9 (15.3)
Number (%) of Patients with at Least One Moderate TEAE	15 (28.8)	8 (10.8)	6 (10.2)

-continued

Overall Summary of Treatment Emergent Adverse Events - Safety Population

	Colchicine Dose		
	High (N = 52) n (%)	Low (N = 74) n (%)	Placebo (N = 59) n (%)
Number (%) of Patients with at Least One Severe TEAE	10 (19.2)	0	1 (1.7)
Number (%) of Patients with a TEAE Discontinuing Study	0	0	0
Number (%) of Patients with a Treatment Emergent SAE	0	0	0

[1]Patients reporting more than one adverse event are only counted once for a given event.

Number (%) of Patients with at Least One Treatment-Emergent Gastrointestinal Adverse Event Recorded on the Diary or the CRF-Safety Population

	Colchicine Dose					
	Standard (N = 52)		Low (N = 74)		Placebo (N = 59)	
Method of Capture	All	Severe	All	Severe	All	Severe
Captured on Adverse Event CRF [1]	40 (76.9) [2]	10 (19.2)	19 (25.7)	0	12 (20.3)	0
Captured on Patient Diary	48 (92.3) [2]	13 (25.0)	32 (43.2) [3]	3 (4.1)	15 (25.4)	2 (3.4)
Captured on Patient Diary or Adverse Event CRF	49 (94.2) [2]	18 (34.6)	33 (44.6)	3 (4.1)	16 (27.1)	2 (3.4)

[1] Gastrointestinal adverse events captured on the AE CRF include the MedDRA preferred terms of "diarrhoea", "nausea", "vomiting", "abdominal pain", or "abdominal pain lower", "abdominal pain upper", "abdominal discomfort", or "dyspepsia".
[2] Statistically significantly different from placebo and from Low-dose colchicine (95% CI of odds ratio does not include "1").
[3] Statistically significantly different from placebo (95% CI of odds ratio does not include "1").

Number (%) of Patients with at Least One Severe TEAE in Any Treatment Group-Safety Population

MedDRA System Organ Class MedDRA Preferred Term	Colchicine Dose High (N = 52) n (%)	Low (N = 74) n (%)	All Colchicine (N = 126) n (%)	Placebo (N = 59) n (%)	Odds Ratio (95% Confidence) High vs. Placebo	Low vs. Placebo	High vs. Low
Number of Patients with at Least One Severe TEAE	10 (19.2)	0	10 (7.9)	1 (1.7)	13.8 (1.7, 112)	—	—
Gastrointestinal Disorders	10 (19.2)	0	10 (7.9)	0	—	—	—
Diarrhea	10 (19.2)	0	10 (7.9)	0	—	—	—
Melaena	1 (1.9)	0	1 (0.8)	0	—	—	—
Nausea	1 (1.9)	0	1 (0.8)	0	—	—	—
Metabolism and Nutrition Disorders	0	0	0	1 (1.7)	—	—	—
Gout	0	0	0	1 (1.7)	—	—	—
Musculoskeletal and Connective Tissue Disorders	1 (1.9)	0	1 (0.8)	0	—	—	—
Pain in Extremity	1 (1.9)	0	1 (0.8)	0	—	—	—

Number (%) of Patients with at Least One Drug-Related Treatment Emergent Adverse Events with an Incidence of ≧2% of Patients in Any Treatment Group

MedDRA System Organ Class MedDRA Preferred Term	Colchicine Dose High (N = 52) n (%)	Low (N = 74) n (%)	Placebo (N = 59) n (%)	Odds Ratio (95% Confidence Intervals) High vs. Placebo	Low vs. Placebo	High vs. Low
Number of Patients with at Least One Drug-Related TEAE	38 (73.1)	21 (28.4)	14 (23.7)	8.7 (3.7, 20.6)	1.3 (0.6, 2.8)	6.9 (3.1, 15.2)
Gastro-intestinal Disorders	38 (73.1)	18 (24.3)	11 (18.6)	11.8 (4.8, 29.0)	1.4 (0.6, 3.3)	8.4 (3.8, 19.0)
Diarrhea	38 (73.1)	16 (21.6)	8 (13.6)	17.3 (6.6, 45.4)	1.8 (0.7, 4.4)	9.8 (4.3, 22.5)
Nausea	7 (13.5)	3 (4.1)	3 (5.1)	2.9 (0.7, 11.9)	0.8 (0.2, 4.1)	3.7 (0.9, 15.0)
Vomiting	8 (15.4)	0	0	—	—	—

As shown in the above tables, standard dose colchicine produced >50% pain reduction at 24 hrs without pain rescue in a greater proportion of patients than did placebo (32.7% vs. 15.5%, p=0.0343; odds ratio 2.64 (95% CI, 1.06, 6.62), and more gastrointestinal side effects than placebo (73.1% vs. 18.6%, odds ratio 11.8 {95% CI, 4.8, 29.0}), in particular more diarrhea than placebo (73.1% vs. 13.6%, odds ratio 17.3 {95% CI, 6.6, 45.4}). Low dose colchicine also produced >50% pain reduction at 24 hrs without pain rescue in a greater proportion of patients than did placebo (37.8% vs. 15.5%, p=0.0046; odds ratio 3.31 (95% CI, 1.41, 7.77)), and more gastrointestinal side effects than placebo (24.3% vs. 18.6%, odds ratio 1.4 {95% CI, 0.7 to 11.9}), but did not significantly differ from placebo with respect to diarrhea (21.6% vs. 13.6%, odds ratio 1.8 {95% CI, 0.7 to 4.4}). Severe diarrhea occurred in 19.2% of patients taking high-dose colchicine while not occurring in the low-dose colchicine group. Vomiting occurred in 15.4% of patients taking high-dose colchicine while not occurring in the low-dose colchicine group.

Based on the primary efficacy variable of ≧50% pain reduction at 24 hrs without pain rescue, the proportion of responders to the standard dose and the low dose colchicine regimens was not significantly different (p=0.5529). The odds ratio for being a responder to standard dose colchicine vs. being a responder to low dose colchicine was 0.80 (95% CI, 0.38, 1.68). The proportion of patients rescued prior to 24 hours for the standard dose, low dose and placebo were 34.6%, 28.4% and 48.3%, respectively.

FIG. **1** summarizes efficacy data from the trial. FIG. **1** shows the fraction of all patients improved at 24 hrs post-first dose, regardless of pain rescue, as a function of the percent improvement in pain for each of the three treatment methods (standard dose, low dose, placebo). For example, 49% of patients taking the low dose achieved at least 40% relief compared to 24% of the patients on placebo.

Standard dose oral colchicine was established to be effective, but burdened by significant diarrhea. In contrast, although low dose colchicine was not significantly different from standard dose colchicine in efficacy, low dose colchicine was not significantly different from placebo with respect to diarrhea. This trial provides a new evidence basis for acute gout treatment, specifically supporting the unexpected superiority of a low dose colchicine dosing regimen of 2 tablets of 0.6 mg followed in 1 hour by 1 tablet. The higher standard dose colchicine dosing regimen did not improve patient outcome, but did increase adverse events.

Example 4

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6-mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day washout. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed C_{min} concentrations at steady state. C_{min} concentrations prior to the morning dose are approximately 12% higher than the C_{min} concentrations prior to the evening dose (Day 23 and Day 24). The mean C_{min} concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 $AUC_{0-\tau}$/Day 1 $AUC_{0-\infty}$] and approximately 1.5 based on Cmax[Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC_{∞} following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in the tables below.

TABLE 10

Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults

	AUC_{0-t} (pg-hr/mL)	AUC_{0-inf} (pg-hr/mL)	C_{max} (pg/mL)	T_{max} (hr)	Kel (1/hr)	$T_{1/2}$ (hr)
N	13	13	13	13	13	13
MEAN	10508.54	12281.90	2470.77	1.50	0.1829	4.95
STDEV	3544.82	4423.34	706.98	0.54	0.0592	4.43
% CV	33.73	36.02	28.61	36.00	32.39	89.54
MEDIAN	10560.90	11451.45	2714.00	1.50	0.1992	3.48
MIN	4812.88	7252.66	1584.00	1.00	0.0359	2.84
MAX	18128.65	23838.48	3977.00	3.00	0.2443	19.29

TABLE 11

Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults

	AUC_{0-t} (pg-hr/mL)	$AUC_{0-\tau}$ (pg-hr/mL)	AUC_{0-inf} (pg/mL)	C_{max} (pg/mL)	C_{min} (pg/mL)	C_{ave} (pg/mL)	T_{max} (hr)	Kel (1/hr)	$T_{1/2}$ (hr)
N	13	13	13	13	13	13	13	13	13
MEAN	43576.96	29056.23	54198.77	3553.15	906.51	1210.68	1.31	0.03	26.60
STDEV	9333.26	4531.30	9214.54	843.45	152.19	188.80	0.60	0.00	4.33
% CV	21.42	15.59	17.00	23.74	16.79	15.59	45.61	16.34	16.26
MEDIAN	41925.10	28452.15	54113.43	3734.00	903.50	1185.51	1.00	0.03	26.51
MIN	29328.78	20791.98	37599.76	1977.00	636.23	866.33	0.50	0.02	20.82
MAX	58265.35	36083.95	67944.65	4957.00	1149.67	1503.50	3.00	0.03	33.65

TABLE 12A

Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults

	Vd/F (L)	CL/F (L/hr)
Colchicine 0.6-mg Single Dose (N = 13)		
Day 1	341 (54.4)	54.1 (31.0)
Colchicine 0.6 mg b.i.d. × 10 days		
Day 25	1150 (18.73)	30.3 (19.0)

CL = Dose/AUC_{0-t} (Calculated from mean values)

Vd = CL/Ke (Calculated from mean values)

2-DMC concentrations were below the LOQ for all subjects. Eight of 13 subjects had at least one measurable 3-DMC concentration (29 total 3-DMC measurable concentrations). 3-DMC concentrations ranged from 0.20 ng/mL (near the LOQ) to 0.45 ng/mL and were observed 1 to 4 hours post-dose. Given these low levels, metabolites are not discussed further herein.

When colchicine was administered in this low-dose regimen, concentrations increased to a maximum of 6.2 ng/mL, occurring 1.81 hours after the initial dose (0.81 hours after the second dose). Most of the subjects (10 of 13 subjects or 77%) experienced a secondary peak within 6 hours after the first of the two doses, attributed to intestinal secretion and re-absorption and/or biliary recirculation.

The terminal elimination half-life was 23.6 hours. A summary of the pharmacokinetic parameter values is provided in in the table below.

TABLE 12

Colchicine Pharmacokinetic Parameter Values after Low-Dose Colchicine (1.8 mg over 2 hours) Administration in Healthy Adults

	C_{max} (pg/mL)	T_{max} (hr)	Total AUC_{0-t} (pg-hr/mL)	Total AUC_{∞} (pg-hr/mL)	K_{el} (1/hr)	CL/F (mL/hr)	V_{area}/F (L)	$t_{1/2}$ (hr)
N	13	13	13	13	13	13	13	13
MEAN	6192.77	1.81	43787.55	52070.06	0.0326	36950.93	1188.72	23.63
STDEV	2433.70	0.38	11437.48	13689.27	0.0100	9993.17	319.56	9.24
% CV	39.30	21.24	26.12	26.29	30.80	27.04	26.88	39.10
MEDIAN	5684.00	2.00	43942.15	50783.77	0.0322	35444.40	1149.35	21.56
MIN	3160.00	1.00	28821.45	34171.00	0.0141	24295.73	774.19	13.80
MAX	11370.00	2.50	58931.99	74087.08	0.0502	52676.24	1724.36	49.20

In the above table, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{0-tau}; and V_d/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_{\infty} \times K_{el}$.

Example 5

Pharmacokinetic Study in Healthy Adults of Low Dose Acute Gout Regimen: 1.8 mg Over 2 Hours

This study was a single-center, single-period, open-label pharmacokinetic study conducted in healthy subjects under fasting conditions. It was designed to characterize the pharmacokinetic profile of a low-dose regimen of colchicine (1.8 mg over 2 hours) used as one of the treatment arms in the randomized, controlled trial in patients with an acute gout flare discussed above.

Thirteen healthy, non-smoking subjects with a mean age of 29.3 years (range 20 to 49 years) and within 15% of ideal body weight were enrolled in this study. Subjects received 2×0.6 mg tablets initially followed by 1×0.6 mg tablet 1 hour later. Blood samples for measurement of colchicine plasma concentrations and metabolites were collected (relative to the first dose of study drug) at pre-dose; 0.5 and 1 hour post-dose (prior to second dose); and 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post-dose. Subjects were confined until 48 hours post-dose and then returned 72 and 96 hours after the first dose for additional blood sampling on an outpatient basis. Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Example 6

Pharmacokinetic Study in Healthy Adults of a Standard-Dose Acute Gout Regimen: 4.8 mg Colchicine Over 6 Hours

This study was a single center, randomized, double-blind, double-dummy pharmacokinetic and exploratory ECG safety study.

With respect to the pharmacokinetic aspect of the study, on Day 1, following a minimum of 10 hours overnight fast, subjects received the appropriate randomized study drug (combination of over-encapsulated active drug or placebo capsules such that the blind was preserved). Those randomized to colchicine received 4.8 mg over 6 hours (initially 2×0.6 mg tablets followed by 1×0.6 mg tablet every hour for six additional doses). Those randomized to moxifloxacin received 1×400 mg tablet. Both dosing regimens were followed by a 4-hour post-dose fast (post-dose fast for colchicine arm started after the first dose of colchicine administered). Blood samples were obtained on Day 1 at the following time points (relative to the first dose of study drug): pre-dose and 1 (prior to second dose), 3 (prior to fourth dose), 6 (prior to final dose), 6.17, 6.33, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 10, 12, 23, 36, 48, 72 and 96 hours post-dose. Subjects were confined until 48 hours post-dose and then returned 72 and 96 hours after the first dose for additional blood sampling on an outpatient basis. Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Eighteen healthy, non-smoking subjects with a mean age of 28.7 years (range 18 to 50 years) and within 15% of ideal

body weight were enrolled in this study. Fifteen subjects were randomized to receive colchicine and 3 subjects were randomized to receive moxifloxacin as a positive control for QTc prolongation. All subjects completed the study according to protocol.

When colchicine was administered as the standard-dose regimen used in the treatment of patients experiencing an acute gout flare, colchicine concentrations increased to a maximum of 6.8 ng/mL (similar to the reported C_{max} in the low-dose regimen) and absorbed approximately 4.5 hours after the initial dose (3.5 hours after the second dose). Most of the subjects (13 of 15 subjects receiving colchicine or 87%) experienced a secondary peak within 6 hours after a single oral dose, attributed to intestinal secretion and re-absorption and/or biliary recirculation. The terminal elimination half-life was 31.38 hours. A summary of the pharmacokinetic parameter values is provided in the table below.

TABLE 13

Mean (% CV) Colchicine Pharmacokinetic Parameter Values after Standard-Dose Colchicine (4.8 mg over 6 hours) Administration in Healthy Adults

	C_{max} (ng/mL)	T_{max} (hr)	Total AUC_{0-t} (ng-hr/mL)	Total AUC_{∞} (ng-hr/mL)	K_{el} (h^{-1})	CL/F (mL/hr)	V_{area}/F (L)	$t_{1/2}$ (hr)
N	15	15	15	15	15	15	15	15
MEAN	6.84	4.47	104.95	118.20	0.0242	43168.87	1876.09	31.38
STDEV	1.30	1.99	24.61	26.01	0.0088	12862.03	456.19	8.36
% CV	18.94	44.65	23.45	22.01	36.59	29.79	24.32	26.65
MEDIAN	6.69	3.12	113.12	126.47	0.0212	37954.71	1902.14	32.76
MIN	4.95	3.12	53.74	61.31	0.0147	31386.01	805.92	15.03
MAX	8.60	7.50	138.24	152.93	0.0461	78287.41	2639.21	47.22

2-DMC concentrations were below LOQ for all subjects. Fourteen of 15 subjects had at least one measurable 3-DMC concentration; the 3-DMC concentrations ranged from 0.25 ng/mL (near the LOQ) to 0.42 ng/mL and were observed 1.12 to 12.12 hours post-dose. Summary mean 3-DMC pharmacokinetic parameter values can be found in the table below. The observed mean 3-DMC C_{max}, AUC_{0-t}, and AUC_{∞} concentrations were approximately 4.7%, 2%, and 4.1% of the observed mean colchicine C_{max}, AUC_{0-t}, AUC_{∞} concentrations, respectively.

TABLE 14

Mean (% CV) 3-DMC Pharmacokinetic Parameter Values after Standard-Dose Colchicine (4.8 mg over 6 hours) Administration in Healthy Adults

	C_{max} (ng/mL) N = 15	T_{max}[1] (h) N = 14	AUC_{0-t} (ng · h/mL) N = 13	AUC_{∞} (ng · h/mL) N = 8	Ke (h^{-1}) N = 8	$t_{1/2}$ (h) N = 8
Standard Dose N = 15	0.32 (16.35)	5.06 (3.12-8.12)	2.09 (40.29)	4.84 (42.73)	0.1418 (60.15)	6.93 (64.35)

[1]T_{max} reported mean (range)

Example 7

Food Effect Study Single Dose vs. COL-PROBENECID® (0.5 mg COLCHICINE/500 mg PROBENECID)

The clinical study of this example was a randomized, single-dose, three-way crossover study testing the bioequivalence of two formulations of colchicine administered under standard fasting conditions, one the 0.6 mgA colchicine formulation of Example 2 (test product) and one a marketed combination product, 0.5 mg colchicine/500 mg probenecid tablets (COL-PROBENECID®, Watson Laboratories, Inc.) (reference product), and the effect of food on the test product by dosing following a high-fat breakfast.

Twenty-eight healthy non-smoking adult volunteers (male and female) and no alternates initiated the study. Subjects received three single doses, in a randomized sequence of three treatment periods. On each occasion, subjects received either one colchicine tablet USP, 0.6 mg (test product) given either with food or in a standard fasting condition or one colchicine 0.5 mg/probenecid 500 mg tablet (reference product) given in a standard fasting condition. Each treatment period was separated by a 14-day washout.

The two dosing conditions were (1) Standard Fasting Conditions (either colchicine tablets USP, 0.6 mg (test A) or reference product, COL-PROBENECID®): 1 tablet of test product (Test A) or reference product with 240 mL of room temperature water after an overnight fast of at least 10 hours; subjects will continue to fast for 4 hours post-dose; and (2) High-fat Breakfast (colchicine tablets USP, 0.6 mg): 1 tablet of test product (Test B) with 240 mL of room temperature water 30 minutes after initiation of a standardized, high-fat and high-calorie breakfast (FDA standard meal) preceded by an overnight fast.

Subjects were confined for at least 15 hours prior to and until at least 24 hours after dosing each period. During each period, subjects returned on four separate occasions for outpatient blood sampling.

No fluid, except that given with drug administration and the standardized high-fat and high-calorie breakfast (FDA standard meal) depending on the randomization, was allowed from 1 hour prior to dose administration until 2 hours after dosing. When fluids were restricted, they will be allowed ad libitum but will generally be controlled.

Dinner was served approximately 13.5 hours prior to dose administration. At 30 minutes before dose administration, those subjects to be dosed after eating (depending on randomization) were served the standardized, high-fat and high-calorie breakfast (FDA standard meal). All subjects fasted for at least 4 hours after dosing. Clear fluids, such as water, were allowed during fasting.

Subjects were served standardized meals and beverages, controlled by the clinic during periods of confinement. Meals were the same in content and quantity during each confinement period. No grapefruit and/or grapefruit containing products or caffeine and/or xanthine containing products were allowed during the confinement portions of the study.

During confinement, only non-strenuous activity was permitted. Following dose administration, subjects remained in a seated or upright position for at least 4 hours to ensure proper gastric emptying and subject safety.

Blood (6 mL) was collected in K2 EDTA vacutainers with samples taken within 1 hour prior to dosing (0 hour) and after dose administration at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours (while confined) and 36, 48, 72, and 96 hours (on an outpatient basis). 1. Colchicine and metabolite plasma concentrations (colchicine, 2-DMC, 3-DMC, and 10 demethylcolchicine) were measured using a validated bioanalytical method.

Pharmacokinetic results comparing the test product under fed and fasting conditions are shown below.

TABLE 15

Pharmacokinetic results of colchicine test product under fed and fasting

Ln-Transformed Data

	Least Squares Mean		Geometric Mean			90% Confidence Interval
PK Variable	Test B	Test A	Test B	Test A	% Ratio	(Lower Limit, Upper Limit)
C_{max} (pg/mL)	7.784	7.781	2402.55	2393.60	100.37	(89.84, 112.14)
AUC_{0-t} (pg/mL-hr)	9.201	9.334	9906.40	11310.90	87.58	(78.07, 98.26)
AUC_{0-inf} (pg/mL-hr)	9.300	9.468	10939.73	12939.64	84.54	(76.73, 93.15)

Geometric means are based on least squares means of Ln-transformed values.

Non-Transformed Data

	Least Squares Mean			90% Confidence Interval
PK Variable	Test B	Test A	% Ratio	(Lower Limit, Upper Limit)
C_{max} (pg/mL)	2486.99	2493.15	99.75	(90.43, 109.07)
AUC_{0-t} (pg/mL-hr)	10438.89	12536.56	83.27	(72.79, 93.74)
AUC_{0-inf} (Pg/mL-hr)	11345.62	13907.83	81.58	(71.53, 91.63)
T_{max} (hr)	1.85	1.35	137.14	(111.11, 163.17)
K_{el} (hr^{-1})	0.1902	0.1520	125.13	(107.67, 142.58)
$T_{1/2}$ (hr)	4.34	6.27	69.17	(45.2, 93.14)

TABLE 16

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fasting conditions

	AUC_{0-t} (pg-hr/mL)	AUC_{0-inf} (pg-hr/mL)	C_{max} (pg/mL)
N	25	24	25
Arithmetic Mean	12589	14113	2503
STDev	6210.729	5595.398	722.049
% CV	48.621	39.648	28.847
Median	11412.80	12756.02	2473.00

TABLE 16-continued

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fasting conditions

	AUC_{0-t} (pg-hr/mL)	AUC_{0-inf} (pg-hr/mL)	C_{max} (pg/mL)
Min	4430.73	6674.96	1291.00
Max	30787.30	27789.51	3989.00

TABLE 17

Descriptive statistics for Pharmacokinetic Parameters for Test Product A (0.6 mg) - Fed conditions

	AUC_{0-t} (pg-hr/mL)	AUC_{0-inf} (pg-hr/mL)	C_{max} (pg/mL)
N	25	22	25
Arithmetic Mean	10491	11404	2497
STDev	4024.804	2895.681	695.091
% CV	38.374	25.392	27.838
Median	9556.25	10964.17	2293.00
Min	6168.53	7128.50	1256.00
Max	26031.15	20101.33	3930.00

Food was observed to have negligible effect on rate of absorption, as indicated by the percent ratio of ln-transformed C_{max} data of 100.37, but decreased the extent of absorption by about 15%, as indicated by the percent ratio of ln-transformed AUC_{0-t} and AUC_{0-inf} values of 87.56 and 84.54, respectively. Under fasted and fed conditions, the mean C_{max} was 2.5 ng/mL. T_{max} was 1.35 hrs under fasted conditions and 1.85 hrs under fed conditions.

Pharmacokinetic results comparing the test product to the reference product are shown in the tables below. The difference in colchicine potency of the test and reference products was corrected by calculating dose-normalized values in the pharmacokinetic parameters.

TABLE 18

Summary of Statistical Analysis Colchicine Test Product A (0.6 mg) - Fasting vs Reference Product C (0.5 mg) - Fasting (Dose Normalized to 0.5 mg) N = 25

Ln-Transformed Data

	Least Squares Mean		Geometric Mean			90% Confidence Interval (Lower Limit, Upper
PK Variable	Test A	Reference C	Test A	Reference C	% Ratio	Limit)
C_{max} (pg/mL)	7.598	7.374	1994.67	1594.51	125.10	(111.97, 139.76)
AUC_{0-t} (pg/mL-hr)	9.151	8.833	9425.75	6858.61	137.43	(122.5, 154.18)
AUC_{0-inf} (pg/mL-hr)	9.286	8.970	10783.03	7863.34	137.13	(124.46, 151.09)

Geometric means are based on least squares means of ln-transformed values.

Non-Transformed Data

	Least Squares Mean			90% Confidence Interval
PK Variable	Test A	Reference C	% Ratio	(Lower Limit, Upper Limit)
C_{max} (pg/mL)	2076.08	1688.54	122.95	(110.07, 135.83)
AUC_{0-t} (pg/mL-hr)	10435.91	8016.44	130.18	(115.25, 145.11)
AUC_{0-inf} ((pg/mL-hr)	11565.28	8230.68	140.51	(126.04, 154.99)
T_{max} (hr)	1.35	1.34	100.11	(74.05, 126.17)
Kel (hr^{-1})	0.1520	0.1970	77.16	(63.69, 90.63)
$T_{1/2}$ (hr)	6.27	3.78	165.89	(126.13, 205.65)

The 0.6 mgA colchicine tablet, formulated as in Example 2, showed enhanced bioavailability over COL-PROBENECID®. The formulation disclosed herein showed a greater rate and extent of absorption than did the COL-PROBENECID®.

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

Embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

We claim:

1. A method of treating a patient having a gout flare, the method consisting of:
- orally administering 1.2 mg colchicine to a human patient at onset of a gout flare; and then
- orally administering 0.6 mg colchicine to the patient about one hour after administering the 1.2 mg colchicine,
- the method providing an apparent total body clearance (C L/F) in a range of 2.4 L/hr to 5.3 L/hr.

2. The method of claim **1**, wherein each said orally administering comprises administering one or more dosage forms each containing 0.6 mg colchicine.

3. The method of claim **2**, wherein the dosage form is a tablet.

4. The method of claim **3** wherein the tablet is an immediate release tablet.

5. The method of claim **1**, wherein the colchicine is administered with or without food.

6. A method of treating a patient having a gout flare, the method consisting of:
- orally administering 1.2 mg colchicine to a human patient at onset of a gout flare; and then
- orally administering 0.6 mg colchicine to the patient about one hour after administering the 1.2 mg colchicine,
- the method providing an apparent total volume of distribution (V_{ared}/F) in a range of 0.77 L/hr to 1.7 L/hr.

7. The method of claim **6**, wherein each said orally administering comprises administering one or more dosage forms each containing 0.6 mg colchicine.

8. The method of claim **7**, wherein the dosage form is a tablet.

9. The method of claim **8**, wherein the tablet is an immediate release tablet.

10. The method of claim **6**, wherein the colchicine is administered with or without food.

11. A method of treating a patient having a gout flare, the method consisting of:
- orally administering 1.2 mg colchicine to a human patient at onset of a gout flare; and then
- orally administering 0.6 mg colchicine to the patient about one hour after the first administration,

the method providing a maximum colchicine blood plasma concentration (C_{max}) in a range of 3.2 to 11.4 ng/mL, and a time after the first administration at which C_{max} is reached (T_{max}) of 1.0 to 2.5 hr.

12. The method of claim **11**, the method further providing an area under the curve of colchicine plasma concentration versus time from time 0 to time t (AUC_{0-t}), where t is the last time point with a measurable colchicine plasma concentration, in a range of 28.8 to 58.9 ng-hr/mL.

13. The method of claim **11**, the method further providing an area under the curve of colchicine plasma concentration versus time from time 0 to time infinity ($AUC_{0-\infty}$) in a range of 34.2 to 74.1 ng-hr/mL.

14. The method of claim **11**, the method further providing an area under the curve of colchicine plasma concentration versus time from time 0 to time t (AUC_{0-t}), where t is the last time point with a measurable colchicine plasma concentration, in a range of 28.8 to 58.9 ng-hr/mL and an area under the curve of colchicine plasma concentration versus time from time 0 to time infinity ($AUC_{0-\infty}$) in a range of 34.2 to 74.1 ng-hr/mL.

15. The method of claim **11**, wherein each said orally administering comprises administering one or more dosage forms each containing 0.6 mg colchicine.

16. The method of claim **15**, wherein the dosage form is a tablet.

17. The method of claim **16**, wherein the tablet is an immediate release tablet.

18. The method of claim **11**, wherein the colchicine is administered with or without food.

19. A method of treating a patient having a gout flare, the method consisting of:

orally administering 1.2 mg colchicine to a human patient at onset of a gout flare; and then

orally administering 0.6 mg colchicine to the patient about one hour after the first administration,

the method providing a mean maximum colchicine blood plasma concentration (C_{max}) in a range of 3.8 to 8.6 ng/mL and a mean time after the first administration at which C_{max} is reached (T_{max}) in a range of 1.4 to 2.2 hr.

20. The method of claim **19**, the method further providing a mean area under the curve of colchicine plasma concentration versus time from time 0 to time t (AUC_{0-t}), where t is the last time point with a measurable colchicine plasma concentration, in a range of 32.4 to 55.2 ng-hr/mL.

21. The method of claim **19**, the method further providing a mean area under the curve of colchicine plasma concentration versus time from time 0 to time infinity ($AUC_{0-\infty}$) in a range of 38.4 to 65.8 ng-hr/mL.

22. The method of claim **19**, the method further providing a mean area under the curve of colchicine plasma concentration versus time from time 0 to time t (AUC_{0-t}), where t is the last time point with a measurable colchicine plasma concentration, in a range of 32.4 to 55.2 ng-hr/mL and a mean area under the curve of colchicine plasma concentration versus time from time 0 to time infinity ($AUC_{0-\infty}$) in a range of 38.4 to 65.8 ng-hr/mL.

23. The method of claim **19**, wherein each said orally administering comprises administering one or more dosage forms each containing 0.6 mg colchicine.

24. The method of claim **23**, wherein the dosage form is a tablet.

25. The method of claim **24**, wherein the tablet is an immediate release tablet.

26. The method of claim **19**, wherein the colchicine is administered with or without food.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,415,396 B1
APPLICATION NO. : 13/452277
DATED : April 9, 2013
INVENTOR(S) : Matthew W. Davis

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specifications

In column 37, line 28, delete "Mix" and insert -- Min --, therefor.

In column 37, line 31, delete "Mix" and insert -- Min --, therefor.

In column 37, line 35, delete "Mix" and insert -- Min --, therefor.

In column 37, line 38, delete "Mix" and insert -- Min --, therefor.

In column 37, line 56, delete "Mix" and insert -- Min --, therefor.

In column 37, line 61, delete "Mix" and insert -- Min --, therefor.

In column 39, line 12, delete "Mix" and insert -- Min --, therefor.

In column 39, line 15, delete "Mix" and insert -- Min --, therefor.

In column 39, line 18, delete "Mix" and insert -- Min --, therefor.

In column 39, line 21, delete "Mix" and insert -- Min --, therefor.

In column 41, line 7, after "(95% Confidence" insert -- Intervals) --.

In column 44, line 43, delete "Kel" and insert -- K_{el} --, therefor.

In column 44, line 58, delete "Kel" and insert -- K_{el} --, therefor.

In column 46, line 22, after "TABLE 12" insert -- B --.

In column 51, line 23, delete "Kel" and insert -- K_{el} --, therefor.

In the Claims

In column 52, line 35, delete "2.4" and insert -- 24 --, therefor.

In column 52, line 35, delete "5.3" and insert -- 53 --, therefor.

In column 52, line 52, delete "0.77 L/hr" and insert -- 770 L --, therefor.

In column 52, line 52, delete "1.7 L/hr" and insert -- 1700 L --, therefor.

Signed and Sealed this
Fourth Day of June, 2013

Teresa Stanek Rea

Teresa Stanek Rea
Acting Director of the United States Patent and Trademark Office

EXHIBIT P

US008440721B2

(12) **United States Patent**
Davis

(10) **Patent No.: US 8,440,721 B2**
(45) **Date of Patent: *May 14, 2013**

(54) **METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT**

(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)

(73) Assignee: **Takeda Pharmaceuticals U.S.A., Inc.**, Deerfield, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/184,704**

(22) Filed: **Jul. 18, 2011**

(65) **Prior Publication Data**

US 2011/0275720 A1 Nov. 10, 2011

Related U.S. Application Data

(63) Continuation of application No. 12/909,171, filed on Oct. 21, 2010, now abandoned, which is a continuation of application No. 12/372,046, filed on Feb. 17, 2009, now Pat. No. 7,820,681.

(60) Provisional application No. 61/138,141, filed on Jan. 14, 2009, provisional application No. 61/152,067, filed on Feb. 12, 2009.

(51) **Int. Cl.**

A01N 37/18	(2006.01)
A61K 31/16	(2006.01)
C07C 233/00	(2006.01)
C07C 235/00	(2006.01)
C07C 237/00	(2006.01)
C07C 239/00	(2006.01)
C07C 211/00	(2006.01)
C07C 205/00	(2006.01)
C07C 207/00	(2006.01)

(52) **U.S. Cl.**
USPC **514/629**; 564/123; 564/308; 564/427; 568/306

(58) **Field of Classification Search** ... 514/629; 564/123, 564/308, 427; 568/306
See application file for complete search history.

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Primary Examiner — Kara R McMillian
(74) *Attorney, Agent, or Firm* — Cantor Colburn LLP

(57) **ABSTRACT**

Methods for concomitant administration of colchicine together with one or more second active agents, e.g., ketoconazole and ritonavir, are disclosed. Such methods reduce the dangers commonly associated with such concomitant administration and provide additional benefits. Methods of notifying health care practitioners and patients regarding appropriate dosing for concomitant administration of colchicine together with second active agents are also provided.

4 Claims, 5 Drawing Sheets

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FIG. 1

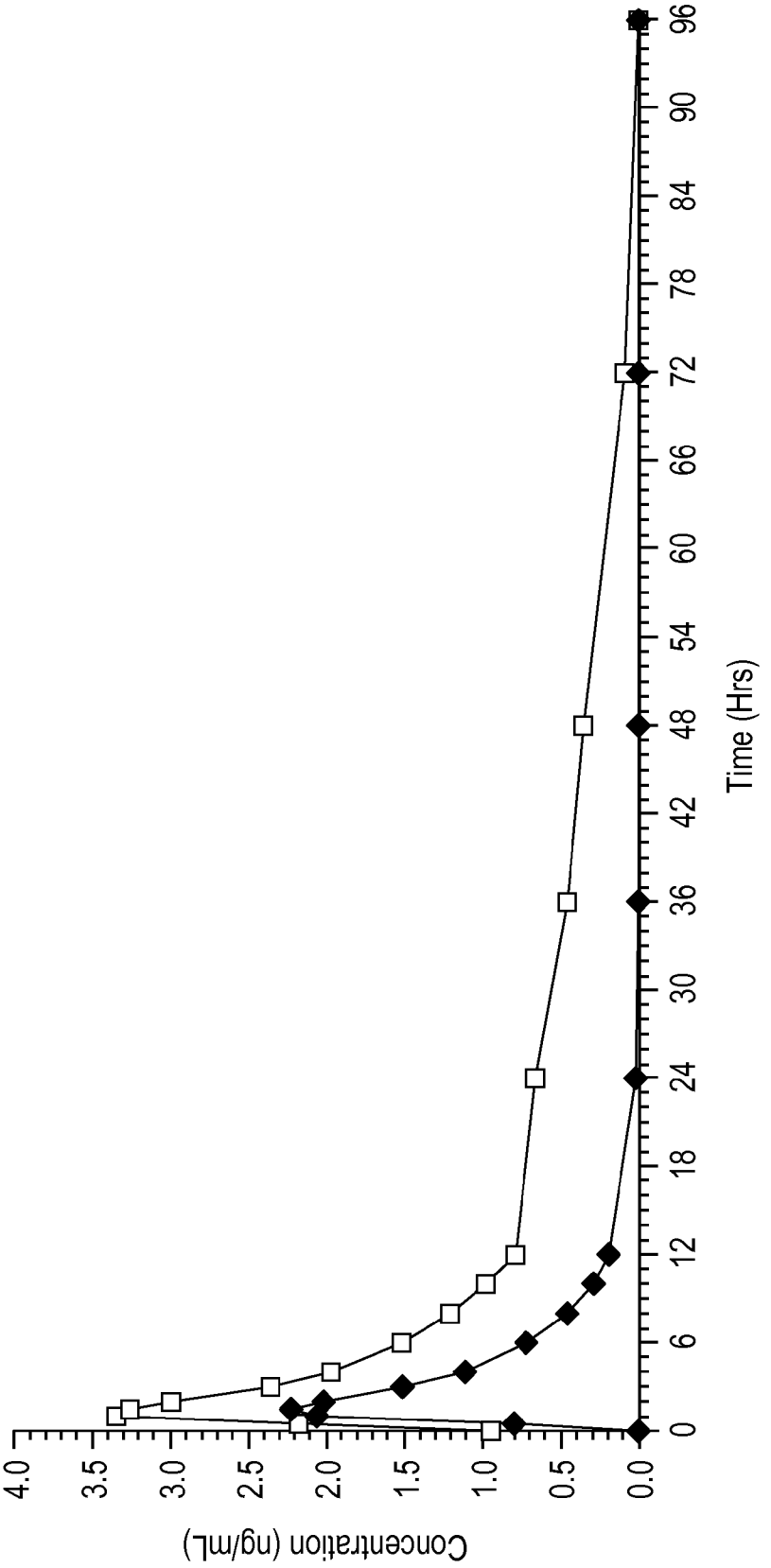

Concentration (ng/mL)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Time (Hrs)
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
90
96

FIG. 2

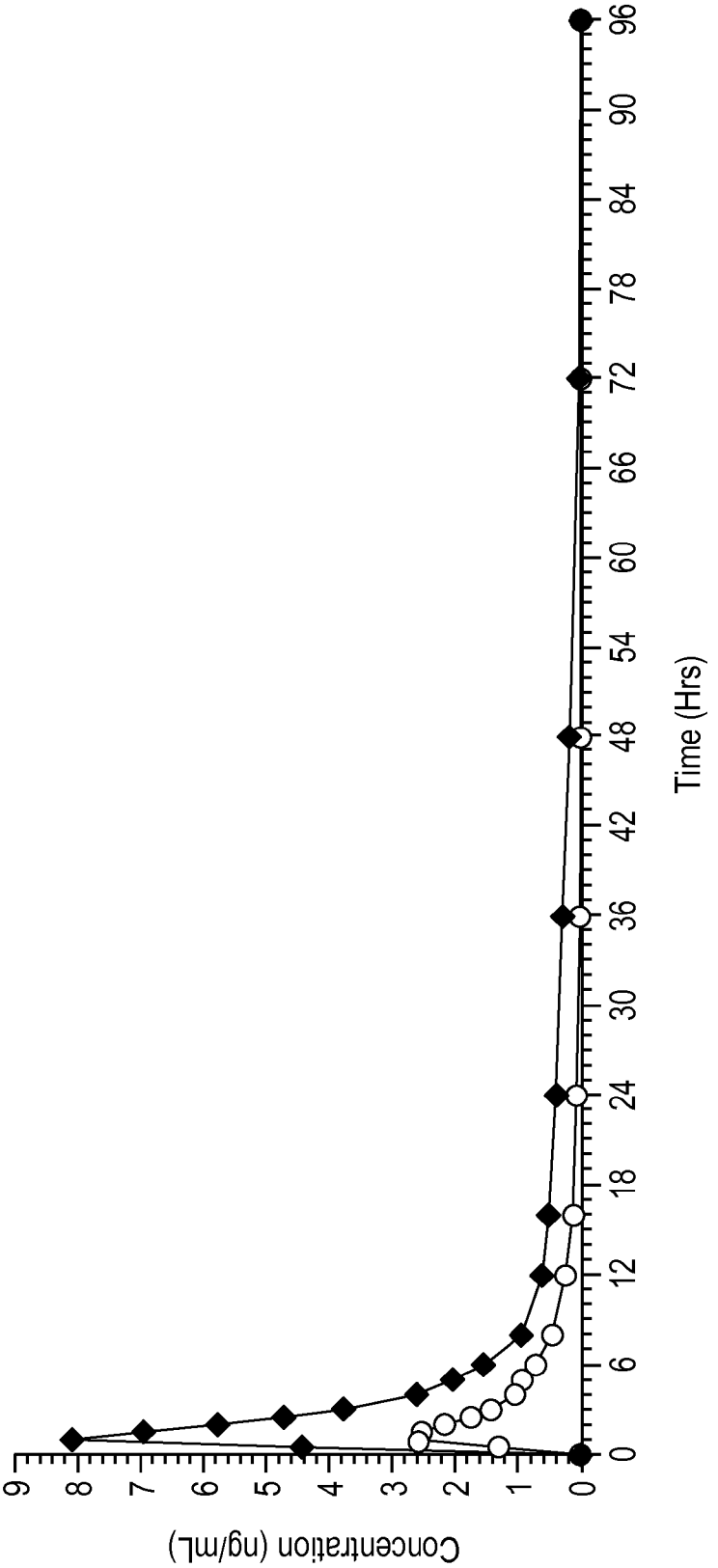

Concentration (ng/mL)
0
1
2
3
4
5
6
7
8
9
Time (Hrs)
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
90
96

FIG. 3

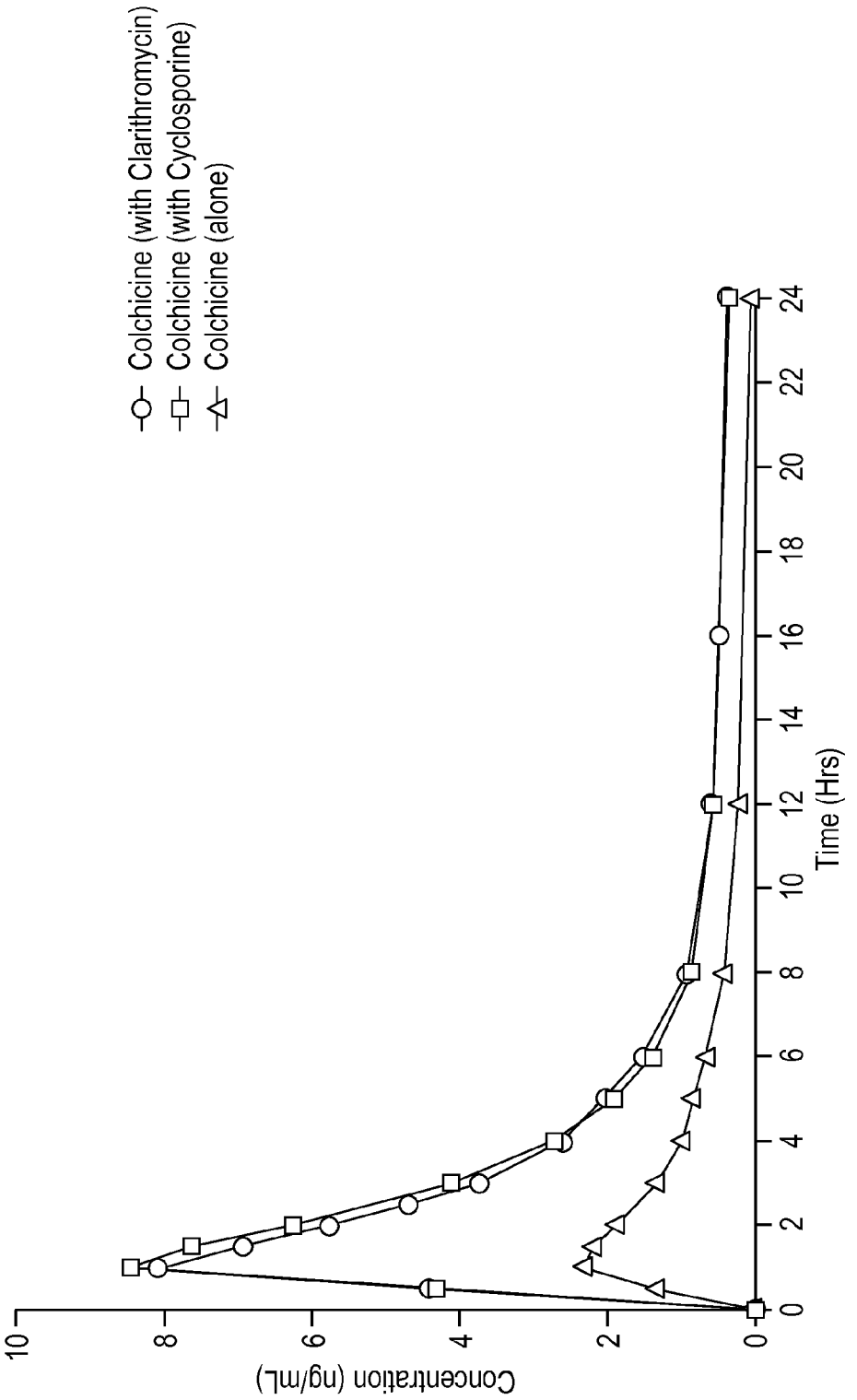

Colchicine (with Clarithromycin)
Colchicine (with Cyclosporine)
Colchicine (alone)
Concentration (ng/mL)
Time (Hrs)
0
2
4
6
8
10
0
2
4
6
8
10
12
14
16
18
20
22
24

FIG. 4

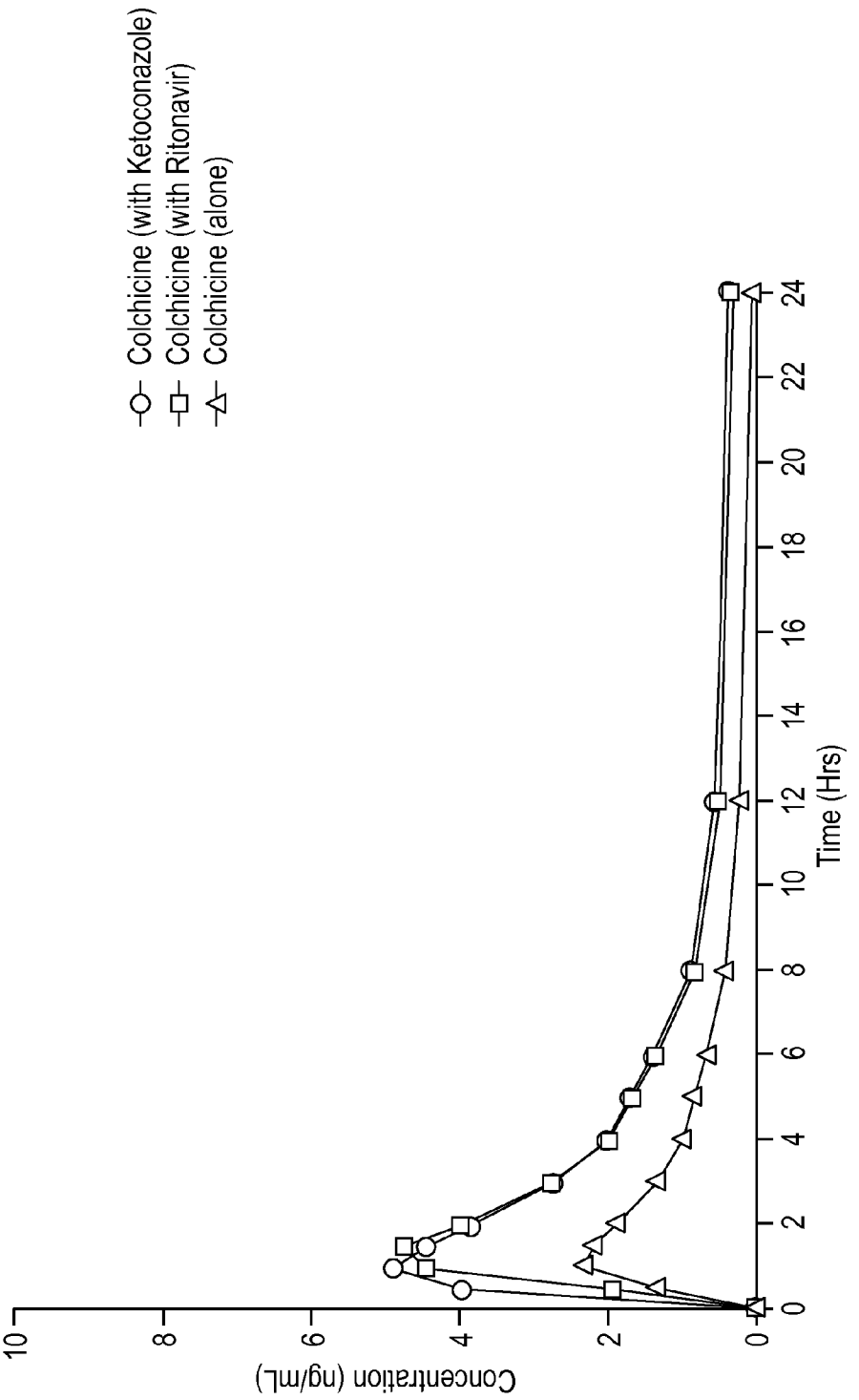
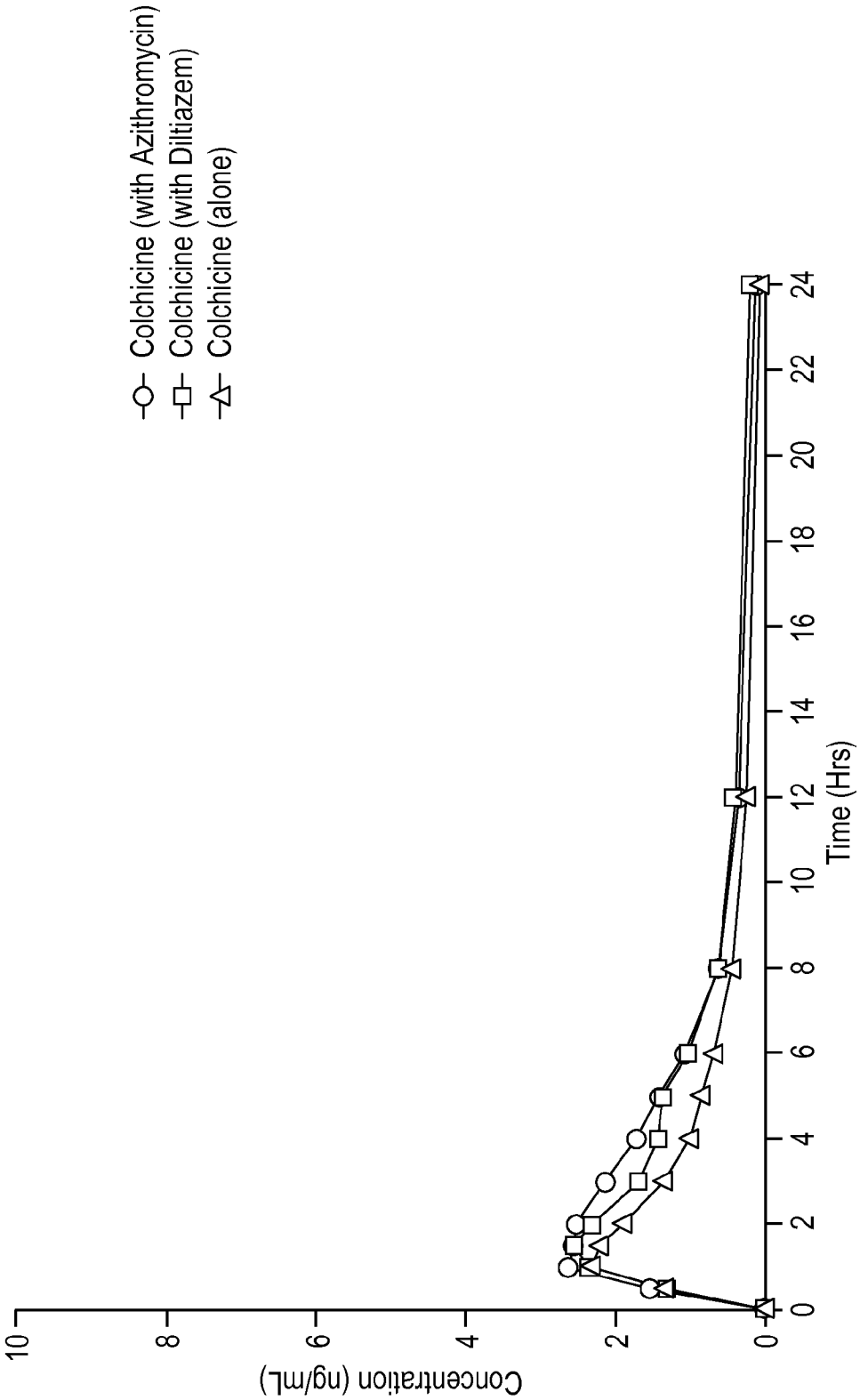

Colchicine (with Ketoconazole)
Colchicine (with Ritonavir)
Colchicine (alone)
Concentration (ng/mL)
0
2
4
6
8
10
Time (Hrs)
0
2
4
6
8
10
12
14
16
18
20
22
24

FIG. 5


Colchicine (with Azithromycin)
Colchicine (with Diltiazem)
Colchicine (alone)
Concentration (ng/mL)
0
2
4
6
8
10
Time (Hrs)
0
2
4
6
8
10
12
14
16
18
20
22
24

METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Continuation U.S. application Ser. No. 12/909,171, filed Oct. 21, 2010, which is a continuation of U.S. application Ser. No. 12/372,046, filed Feb. 17, 2009, now U.S. Pat. No. 7,820,681, which claims priority from U.S. Provisional Application Ser. Nos. 61/138,141 filed Dec. 17, 2008 and 61/152,067 filed Feb. 12, 2009, all of which are hereby incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

This disclosure relates to methods allowing for the co-administration of colchicine together with one or more second active agents for therapeutic purposes with improved safety compared to prior methods of administration.

BACKGROUND

Colchicine, chemical name (−)-N-[(7S, 12aS)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is an alkaloid found in extracts of *Colchicum autumnale, Gloriosa superba*, and other plants. It is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, resulting in effects in cells with high turnover rates such as those in the gastrointestinal tract and bone marrow. The primary adverse side effects of colchicine therapy include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a narrow therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of many other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid in the joints. Such a build up is typically due to an overproduction of uric acid, or to a reduced ability of the kidney to excrete uric acid. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmness, and stiffness in the affected joint. Low-grade fever may also be present. A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this manner, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for prophylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

Cytochrome p450 (CYP) enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes and different CYP isozymes may preferentially metabolize different drugs. The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and second active agents. While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylchochicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity.

P-glycoprotein (P-gp) is an ATP-dependent cell surface transporter molecule that acts as an ATPase efflux pump for multiple cytotoxic agents, including colchicine. P-gp actively pumps certain compounds, including drugs such as colchicine, out of cells. P-gp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Since colchicine acts intracellularly, the combined effects of CYP3A4 inhibition and P-gp inhibition by second active agents that also interact with CYP3A4 and P-gp can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant second agent administration. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

There accordingly remains a need for improved methods for administering colchicine to individuals who are concomitantly being treated with second active agents so as to reduce the possibility of colchicine toxicity while maintaining the sometimes life-saving advantages of being able to administer the two (or more) agents concomitantly. The present disclosure addresses this need and provides further advantages.

SUMMARY

In one embodiment, a method of treating an individual in need of treatment with colchicine comprises concomitantly administering to the individual colchicine and another drug, for example, ketoconazole or ritonavir or cyclosporine, wherein the colchicine is administered as a dosing regimen with a starting colchicine dose of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg. According to another embodi-

ment, the other drug is, for example, verapamil or diltiazem, and the starting colchicine dose during coadministration with the other drug is no more than about 1.2 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours.

In another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in a individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-t} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max}, AUC_{0-t}, AUC_{0-inf}, or clearance in a matched individual not administered concomitant ketoconazole.

In yet another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in an individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-t} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max}, AUC_{0-t}, or clearance in a matched individual not administered concomitant ritonavir.

In another embodiment, a method for using colchicine comprises a pharmacy receiving a prescription for colchicine for a patient who is concomitantly being treated with ketoconazole or ritonavir or verapamil, and the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by: entering, into a first computer readable storage medium in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient, wherein the computer has been programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that ketoconazole or ritonavir or verapamil is being concomitantly administered to the patient, wherein, upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that that ketoconazole or ritonavir is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a dose suitable for the patient if the patient were not receiving concomitant ritonavir.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole.

A method of treating an individual in need of treatment for gout flares, comprises concomitantly administering colchicine and azithromycin, and carefully monitoring the individual for potential toxicity. The method further comprises adjusting the dose of colchicine or azithromycin as necessary to avoid adverse side effects.

A method of treating an individual with colchicine comprises concomitantly administering colchicine and verapamil, and carefully monitoring the individual for signs and symptoms of adverse side effects. The method further comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is about 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for a patient if the patient were not receiving concomitant verapamil.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ♦=day 1, □=day 25. See Example 1.

FIG. **2** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=23, ●=colchicine alone, ♦=colchicine plus clarithromycin. See Example 2.

FIG. **3** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus clarithromycin, ■=colchicine plus cyclosporine.

FIG. **4** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ketoconazole and steady-state ritonavir in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus ketoconazole, ■=colchicine plus ritonavir.

FIG. **5** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus azithromycin, ■=colchicine plus diltiazem.

These and other embodiments, advantages and features of the present invention become clear when detailed description is provided in subsequent sections.

DETAILED DESCRIPTION

Disclosed herein are methods for safely administering colchicine concomitantly with a second active agent, wherein the second active agent is a CYP3A4 inhibitor, a P-gp inhibitor, or both. Exemplary second active agents that are CYP3A4 and P-gp inhibitors are azithromycin, ketoconazole, ritonavir, diltiazem, verapamil and cyclosporine. It has now been discovered that certain reduced or limited colchicine dosage amounts, when administered with concomitantly administered recommended dosage amounts of second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosages in the absence of concomitant administration with the second active agent. Thus, colchicine and second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, can be administered concomitantly with improved safety when colchicine is administered as disclosed herein.

Without being held to theory, it has been hypothesized by the inventors herein that P-gp inhibition is more important in the elimination of colchicine than CYP3A4 inhibition. The CYP3A4 and P-gp inhibition potential of clarithromycin, azithromycin, ketoconazole, ritonavir, diltiazem and cyclosporine are given in Table 1. Based on their level of P-gp inhibition, it was predicted that clarithromycin and cyclosporine will increase colchicine concentrations more than ketoconazole or ritonavir, which will increase colchicine levels more than verapamil, azithromycin or diltiazem. The results presented herein confirm this hypothesis.

TABLE 1

CYP3A4 and P-gp inhibition potential of second active agents

Drug	CYP3A Inhibition potential	P-gp Inhibition potential
Clarithromycin	+++++	+++++
Cyclosporine	+++++	+++++
Ketoconazole	+++++	+++
Ritonavir	+++++	+++
Verapamil	++	++
Diltiazem	+	+
Azithromycin	+	+

Ritonavir (Norvir®, Abbott Laboratories) is an inhibitor of Human Immunodeficiency Virus (HIV) protease and is approved for the treatment of HIV-infection when used as part of a highly active antiretroviral therapy (HAART) regimen at the recommended dose of 600 mg twice daily. Although a very potent and effective protease inhibitor at the recommended dose, ritonavir is not well tolerated by HIV-infected patients at the approved dose and therefore, is generally not used clinically as a sole, therapeutic protease inhibitor within a HAART regimen. Rather, ritonavir is used more often as a pharmacokinetic enhancer or 'boosting agent' when combined with other approved protease inhibitors that are CYP3A4 and P-gp substrates and also have inherent bioavailability issues, such as poor bioavailability due to first pass effect. Improving the pharmacokinetic disposition of other protease inhibitors is possible due to the potent CYP3A4 and P-gp inhibitory activity ritonavir possesses. Sub-therapeutic ritonavir doses are used to achieve pharmacokinetic enhancement of the co-administered protease inhibitors; typically 100 mg of ritonavir administered twice daily is the ritonavir dose used in combination with the primary protease inhibitor. This low-dose ritonavir regimen boosts the bioavailability of the second protease inhibitor without contributing significantly to the adverse event profile of the HAART regimen.

Cyclosporine (Neoral®, Novartis Pharmaceuticals Corporation) is the active principle in Neoral® an oral formulation that immediately forms a microemulsion in an aqueous environment. Cyclosporine is indicated for kidney, liver, and heart transplantation; rheumatoid arthritis and psoriasis. Cyclosporine is extensively metabolized by the CYP3A4 enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents.

Ketoconazole is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole is a potent inhibitor of the CYP3A4 enzyme system. Co-administration of ketoconazole and drugs primarily metabolized by the CYP3A4 enzyme may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse side effects.

Azithromycin is a macrolide antibiotic indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in specific conditions. Azithromycin remains the sole agent developed and marketed within the azalide macrolide subclass. Due to its dibasic structure, azithromycin has demonstrated unique pharmacokinetic properties that differ significantly from those of classic macrolide agents. Azithromycin's pharmacokinetics are characterized by low concentrations in serum, secondary to rapid and significant uptake by fibroblasts and acute reactant cells such as polymorphonuclear leukocytes (PMNs), monocytes, and lymphocytes. Azithromycin is a weak to moderate CYP3A4 inhibitor.

Diltiazem (Cardizem® CD, Biovail Pharmaceuticals, Inc. [Biovail]) is an extended-release (ER) calcium ion influx inhibitor available in blue capsules, each containing 240 mg diltiazem hydrochloride for oral administration. Diltiazem ER capsules are indicated for the treatment of hypertension and the management of chronic stable angina and angina due to coronary artery spasm. Diltiazem is a CYP3A4 and P-gp inhibitor.

Verapamil HCl ER (Mylan Pharmaceuticals, Inc.) is a calcium ion influx inhibitor available in a pale green, capsule shaped, film-coated tablets, each containing 240 mg verapamil hydrochloride for oral administration. Verapamil HCl ER tablets are indicated for the management of hypertension. Verapamil HCl ER is a potent CYP3A4 and P-gp inhibitor.

In one embodiment, colchicine is administered to an individual suffering from a condition treatable with colchicine, and the concomitant second active agent (e.g., ketoconazole, ritonavir, cyclosporine, verapamil, or diltiazem or any other CYP3A4 or P-gp inhibitor) is administered concurrently while the colchicine administration is reduced, or the individual has recently completed a dosing regimen of the second active agent, in which case the colchicine administration may still be reduced for a period of time.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., ketoconazole, ritonavir, or cyclosporine) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional

colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose is about 0.3 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 0.6 mg, and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., verapamil or diltiazem) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 1.2 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg or 0.6 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or 1.2 mg, and each additional colchicine dose is about 0.3 mg or 0.6 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 1.2 mg, and each additional colchicine dose, if any, is about 0.3 mg or 0.6 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, the second active agent is ketoconazole or ritonavir. In one embodiment, the ketoconazole is administered to the individual at a dosage of about 200 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the ritonavir is administered to the individual at a dosage of about 200 to 1200 mg daily (e.g., in 2×100 mg doses or 2×600 mg doses) and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In an exemplary regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. More preferably, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

In one embodiment, the second active agent (e.g., ketoconazole or ritonavir or cyclosporine) is administered to the individual before the colchicine is administered to the individual, and wherein the administration of second active agent is terminated no more than about fourteen days prior to the initiation of colchicine administration. For example, the method comprises administering colchicine to an individual also taking a second active agent (e.g., ketoconazole or ritonavir or cyclosporine), or having completed treatment with the second active agent within the prior 14 days, the individual being administered a single dose of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period. According to this embodiment if the second active agent is instead verapamil or diltiazem, if the second active agent is terminated no more than about fourteen days prior to the initiation of the colchicine administration to treat a gout flare, the single dose of colchicine is about 1.2 mg not to be repeated within a 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-t} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max}, AUC_{0-t}, or clearance in the same or a matched individual when not being administered a concomitant ketoconazole. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ketoconazole is about 200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In yet another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-t} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max}, AUC_{0-t}, or clearance in the same or a matched individual when not being administered concomitant ritonavir. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ritonavir is about 200 to about 1200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In one embodiment, a method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ritonavir. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodi-

ment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ritonavir is, for example, 200 mg per day. In one embodiment, the ritonavir is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ritonavir is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ketoconazole is, for example, 250 mg per day. In one embodiment, the ketoconazole is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ketoconazole is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of cyclosporine, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant cyclosporine. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once every other day adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of cyclosporine can be various dosage strengths administered per day, and can be administered as an oral preparation, topically, or intravenously. In one embodiment, the cyclosporine is administered to the patient before the colchicine is administered to the patient, and wherein the administration of cyclosporine is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

In another embodiment, colchicine is concomitantly administered with azithromycin. Concomitant administration of azithromycin with colchicine increases exposure to colchicine approximately 46% and thus has the potential to produce colchicine toxicity. During concomitant use of azithromycin and colchicine, the physician should carefully monitor individuals for any signs or symptoms of colchicine toxicity. Additionally, dosing adjustments to either the colchicine and/or the azithromycin may be necessary to avoid adverse side effects.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant verapamil. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduced from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 1.2 mg. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is about one-third the intended daily dosage amount. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 1.2 mg, given, for example, in two 0.6 mg doses. In one embodiment, the verapamil is administered to the patient before the colchicine is administered to the patient, and wherein the administration of verapamil is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any

0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

Disclosed herein are specific dosage reductions of colchicine that improve safety when colchicine is co-administered with certain active agents. The dose of colchicine recommended for administration without co-administration of certain other active agents, such as CYP3A4 or P-gp inhibitors, is referred to as an intended daily dosage amount. The reduced or modified daily dosage amount determined from the experiments presented herein is referred to as an adjusted daily dosage amount. An adjusted daily dosage amount is thus a daily dosage amount that can be safely co-administered with a second active agent as disclosed herein. A dose adjustment is thus a dose of colchicine and does not include cessation of colchicine, that is, a dose of 0 mg of colchicine.

In these and other embodiments, the colchicine-responsive condition is gout (e.g., a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behçet's disease. In some embodiments, the treatment with colchicine is either palliative or prophylactic. The gout may be acute gout, e.g. a gout flare, or chronic gout.

Acute Gout

Acute gout, or gout flares, can be treated according to the following treatment schedule. This table indicates the original, or intended, dose, i.e., the dose of colchicine recommended absent concomitant administration of the drugs listed below. This table also presents the dose adjustment of the present invention, or the recommended colchicine dose to be administered when the strong and moderate CYP3A4 and P-gp inhibitors are administered concomitantly with colchicine when the patient is being treated for acute gout, or an acute gout flare.

	Colchicine Dose Recommendation	
Drug	Original Intended Dose (Total Dose)	Dose Adjustment
Strong CYP3A4 Inhibitors	Regimen Reduced by Two Thirds	
Erythromycin Ketoconazole Ritonavir	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days.
Moderate CYP3A4 Inhibitors	Regimen Reduced by One Third	
Diltiazem Verapamil	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days.	1.2 mg (2 tablets) × 1 dose. Dose to be repeated no earlier than 3 days.
Strong P-gp Inhibitors	Regimen Reduced by Two Thirds	
Cyclosporine	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days.

Chronic Gout

For chronic gout, an original intended daily dosage amount is 1.2 mg or 6 mg. Alternatively, an intended daily dosage amount of chronic gout can be as much as 2.4 mg per day. The daily dosage amount for chronic gout can be administered at one time or dosed at intervals throughout the day, e.g. twice daily, three times daily, or four times daily.

Chronic gout, with and without a concomitant dose of another drug, can be treated according to the following treatment schedule:

Colchicine Dose Adjustment for Co-administration with Interacting Drugs If No Alternative Available

	Colchicine Dose Recommendation	
Drug	Original Intended Dose	Dose Adjustment
Clarithromycin	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Cyclosporine	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Erythromycin	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Ritonavir	0.6 mg twice daily	0.6 mg once daily
	0.6 mg once daily	0.3 mg once daily

Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) can be treated according to the following intended daily dosing schedule:

	Daily dosage amount	
Age	Usual	Maximum
Adults and children >12 years	1.2 mg	2.4 mg
Children >6 to 12 years	0.9 mg	1.8 mg
Children 4 to 6 years	0.3 mg	1.8 mg

When colchicine is given to patients with FMF concomitantly with other drugs, the adjusted (reduced) dosage amount of colchicine, according to this embodiment, is provided in the table below:

Concomitant Drug Class or Food	Noted or Anticipated Outcome	Clinical Comment
Strong CYP3A4 Inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	Significant increase in colchicine plasma levels[1]; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated.
Moderate CYP3A4 inhibitors: amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil	Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	Use colchicine with caution at reduced maximum dose of 0.6 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use a maximum dose of 0.3 mg twice daily.
Strong P-gp Inhibitors e.g. Cyclosporine, ranolazine.	Significant increase in colchicine plasma levels[1]; fatal colchicine toxicity has been reported with cyclosporine, a strong P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong P-gp inhibitors.	Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated.

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to individuals. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067,524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

In one aspect, one such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A4 or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a second active agent (e.g., ketoconazole or ritonavir) is being concomitantly administered to the patient

and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert is preferably issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In one aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier indicating that the ketoconazole is prescribed so that 200 mg of ketoconazole is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another preferred aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

A preferred dosing regimen calls for ingestion of colchicine to be continued until a total of no more than 1.2 mg or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is to be stopped, e.g., for at least 2, 3, 4, 5, 6, or 7 days, or until a subsequent acute gout flare, or the first sign of a subsequent gout flare, occurs.

In another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier indicating that the ritonavir is prescribed so that 200 or 1200 mg of ritonavir is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

Also disclosed herein is a dosage adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly treated with a second active agent. The second active agent may be, for example, ritonavir, ketoconazole, cyclosporine, verapamil, or diltiazem. The method comprises determining a first colchicine dosing regimen (the colchicine dosing regimen suitable for administration in the absence of co-administration with a second active agent, which dosing regimen may consist of one or more doses of colchicine); and determining a second active agent dosing regimen; and administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient according to a second colchicine dosing regimen, which may consist of one or more reduced colchicine doses. The second colchicine dosing regimen is a fraction of the first colchicine dosing regimen, where the fraction is obtained by administering reduced colchicine doses or by reducing the frequency of colchicine doses, and wherein the fraction is less than or equal to about ⅔ or less than or equal to about ½ or less than or equal to about ⅓.

According to this embodiment, upon the administering the second active agent to the patient at the second active agent

dosing regimen while concomitantly administering colchicine to the patient at the second colchicine dosing regimen, the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from 1/12, 1/6, 1/4, 1/3, 5/12, and 1/2, more preferably, the fraction is 1/3 or 1/2. In one embodiment, if the second colchicine dosing regimen comprises a "first" colchicine dose, and one or more "subsequent" colchicine doses, each subsequent colchicine dose may be the same as the first dose, or a fraction of the first dose. The fraction is selected from about 1/12, about 1/6, about 1/4, about 1/3, about 5/12, about 1/2, and about 7/12, e.g., about 1/2 or about 2/3. In one example, the second colchicine dosing regimen is once-a-day, twice-a-day, three-times-a-day or four-times-a-day. In a variation of this example, the initial treatment day in, a second colchicine dosing regimen that lasts for more than one day, has one more dose administered than are administered each subsequent day.

Preferably the second active agent is selected from ketoconazole, cyclosporine, ritonavir, verapamil, or diltiazem. The specific conditions are selected from gout, FMF, thrombocytopenic purpura, and Behçet's disease. In one embodiment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis, or prevention, of flares. In another embodiment, the fraction of colchicine administered to the patient concomitantly with a second active agent that is a CYP3A4 or P-gp inhibitor is 1/3 or 1/2 the original intended amount of colchicine and treatment with colchicine is initiated subsequent to or at the same time as initiation of treatment with the second active agent.

Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. Preferably, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a P-gp inhibitor and colchicine to the patient. Exemplary P-gp inhibitors include ketoconazole and ritonavir. Preferred dosages of the P-gp inhibitor for this purpose correspond to those called for in the prescribing information for the drug in question. For ketoconazole, an exemplary dosage is 200 mg per day. For ritonavir, an exemplary dosage is 200 or 1200 mg per day. Specific colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6 mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day washout. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchciine (3-DMC) concentration, which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed Cmin concentrations at steady state. Cmin concentrations prior to the morning dose are approximately 12% higher than the Cmin concentrations prior to the evening dose (Day 23 and Day 24). The mean Cmin concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 $AUC_{0-\tau}$/Day 1 $AUC_{0-\infty}$] and approximately 1.5 based on Cmax [Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC∞ following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in Tables 3-5.

TABLE 3

Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13)

	MEAN	STDEV	% CV	MEDIAN	MIN	MAX
AUC_{0-t} (pg-hr/mL)	10494.66	3544.08	33.77	10560.90	4812.88	18091.85
AUC_{0-inf} (pg-hr/mL)	12268.18	4422.08	36.05	11451.45	7252.66	23801.68
Cmax (pg/mL)	2450.15	702.11	28.66	2480.00	1584.00	3977.00
Tmax (hr)	1.50	0.54	36.00	1.50	1.00	3.00
K_{e1} (1/hr)	0.1829	0.0592	32.38	0.1992	0.0359	0.2443
$T_{1/2}$ (hr)	4.95	4.43	89.54	3.48	2.84	19.29

TABLE 4

Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13)

	MEAN	STDEV	% CV	MEDIAN	MIN	MAX
AUC_{0-t} (pg-hr/mL)	43576.96	9333.26	21.42	41925.10	29328.78	58265.35
$AUC_{0-\tau}$ (pg-hr/mL)	20366.61	3322.12	16.31	20423.08	13719.18	25495.25
AUC_{0-inf} (pg-hr/mL)	54198.77	9214.54	17.00	54113.43	37599.76	67944.65
C_{max} (pg/mL)	3553.15	843.45	23.74	3734.00	1977.00	4957.00
C_{min} (pg/mL)	906.51	152.19	16.79	903.50	636.23	1149.67
C_{ave} (pg/mL)	1697.22	276.84	16.31	1701.92	1143.26	2124.60
T_{max} (hr)	1.31	0.60	45.61	1.00	0.50	3.00
K_{e1} (1/hr)	0.0267	0.0044	16.34	0.0261	0.0206	0.0333
$T_{1/2}$ (hr)	26.60	4.33	16.26	26.51	20.82	33.65

TABLE 5

Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults

	Vd/F (L)	CL/F (L/hr)
Colchicine 0.6-mg Single Dose (N = 13)		
Day 1	341 (54.4)	54.1 (31.0)
Colchicine 0.6 mg b.i.d. × 10 days		
Day 25	1150 (18.73)	30.3 (19.0)

CL = Dose/AUC_{0-t} (Calculated from mean values)

Vd = CL/Ke (Calculated from mean values)

In tables, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total $AUC0-_{tau}$; and V_d/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_{\infty} \times K_{el}$). FIG. **1** shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults.

Example 2

Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose. When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared to when colchicine is given alone: the mean C_{max} and AUC_{0-t} concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (VA) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine administered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in Table 5.

TABLE 6

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults

	Arithmetic Mean (% CV)	
Parameter (units)	Colchicine (N = 23)	Colchicine + Clarithromycin (N = 23)
AUC_{0-t} (ng · hr/mL)	12.37 (37.64)	41.95 (23.31)
AUC_{0-inf} (ng · hr/mL)	15.53 (49.6)	52.62 (22.84)
C_{max} (ng/mL)	2.84 (30.97)	8.44 (17.63)
T_{max} (hr)*	1.50 (0.50-2.00)	1.00 (0.50-2.00)
CL/F (L/hr)	46.8 (43.68)	12.0 (23.75)

FIG. **2** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults. Based on the foregoing data, it is concluded that the dose of colchicine co-administered with clarithromycin should be reduced by ⅔.

Example 3

Clinical Drug-Drug Interaction Study of Colchicine and Cyclosporine

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with cyclosporine on Day 15. Cyclosporine was administered as a single-dose (1×100 mg capsule) on the morning of Day 15. A 14 day washout period was completed after the first colchicine dose on Day 1 and prior to the co-administration of colchicine and cyclosporine doses on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 15. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects were then return to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 16-19 (Period 2). Cyclosporine plasma concentrations were not measured.

TABLE 7

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults

	Arithmetic Mean (% CV)	
Parameter (units)	Colchicine (N = 23)	Colchicine + Cyclosporine (N = 23)
AUC_{0-t} (ng · hr/mL)	12.55	39.83
AUC_{0-inf} (ng · hr/mL)	15.00	47.31
C_{max} (ng/mL)	2.72	8.82

TABLE 7-continued

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults

	Arithmetic Mean (% CV)	
Parameter (units)	Colchicine (N = 23)	Colchicine + Cyclosporine (N = 23)
T_{max} (hr)*	1.15	1.13
CL/F (L/hr)	48.24	13.42

FIG. **3** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with cyclosporine should be reduced by approximately ½ to ¾.

Example 4

Clinical Drug-Drug Interaction Study of Colchicine and Ritonavir

An open-label, non-randomized, single-center, one-sequence, two-period drug interaction study was conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

All subjects received a single 0.6-mg dose of colchicine on Day 1 administered under standard fasting conditions, followed by a 14-day washout period completed on an outpatient basis. At discharge on Day 2, study subjects were instructed to return to the clinical site on the mornings and evenings of Days 15 through 18 to receive two daily dosage amounts of ritonavir (1×100 mg ritonavir capsule twice daily (every 12 hours) on Days 15-18) in a 'directly-observed' fashion; after taking the first dose of ritonavir, subjects remained in the clinic for observation for 1 hour post-dose administration on Day 15. On the evening of Day 18, study participants remained at the clinic for their final study confinement period. In the morning on Day 19, study subjects received a single 0.6 mg colchicine dose with a single 100 mg ritonavir dose and study subjects received the final 100 mg ritonavir dose 12 hours later in the evening on Day 19 under standard fasting conditions.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ritonavir plasma concentrations were not measured.

TABLE 8

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonavir in Healthy Adults: ln-transformed data

	Colchicine Alone	Colchicine + Ritonavir	% Ratio
C_{max} (pg/mL), geometric mean	1798.37	4835.39	268.88
AUC_{0-t} (pg · h/mL), geometric mean	7642.71	27793.08	363.65
AUC_{∞} (pg · h/mL), geometric mean	9551.74	33771.36	353.56

TABLE 9

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonavir in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Ritonavir (N = 18)	Colchicine Alone (N = 18)
AUC_{0-t} (ng · hr/mL)	29.05 (30.76)	8.41 (47.46)
$AUC_{0-\infty}$ (ng · hr/mL)	35.28 (29.79)	10.41 (45.48)
C_{max} (ng/mL)	4.99 (25.18)	1.87 (28.19)
T_{max} (hr)	1.5 (1-1.5)	1 (0.5-1.5)
CL/F (L/hr)	18.59 (31.58)	67.93 (39.47)

Following exposure to 100 mg b.i.d.×5 days, there was a significant increase in exposure to a single 0.6-mg colchicine (approximately 245%). Mean peak colchicine concentration increased by approximately 170%. Total apparent oral clearance was decreased by 70% with co-administration. T_{max} is not affected. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. **4** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ritonavir should be reduced by approximately ½.

Example 5

Clinical Drug-Drug Interaction Study of Colchicine and Ketoconazole

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with ketoconazole on Day 19 (AM dose). Ketoconazole was administered for 5 consecutive days [200 mg twice daily (every 12 hours)] beginning on the morning of Day 15, with the last 200 mg ketoconazole dose administered on the evening on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects will be confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects then returnee to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ketoconazole plasma concentrations were not measured.

TABLE 10

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults: ln-transformed data

	Colchicine Alone	Colchicine + Ketoconazole	% Ratio
C_{max} (pg/mL), geometric mean	2598.28	5078.50	195.46
AUC_{0-t} (pg · h/mL), geometric mean	11087.99	33223.80	299.64
AUC_{∞} (pg · h/mL), geometric mean	13185.92	42143.00	319.61

TABLE 11

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults

	Arithmetic Mean (% CV)	
Parameter (units)	Colchicine (N = 23)	Colchicine + Ketoconazole (N = 23)
AUC_{0-t} (pg · hr/mL)	11988.61	34382.82
AUC_{0-inf} (pg · hr/mL)	14314.09	43688.90
C_{max} (pg/mL)	2779.08	5266.92
T_{max} (hr)*	1.00	1.02
CL/F (L/hr)	49301.09	14797.94

*Median (Range) for T_{max}

Following administration of ketoconazole 200 mg b.i.d.×5 days, there was a significant increase in exposure to a single oral dose of colchicine 0.6 mg (C_{max} and AUC_{0-t} increased by 90% and 190%, respectively, and $AUC_{0-\infty}$ increased by about 205%). Total apparent oral clearance decreased by 70% with co-administration. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. **4** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ketoconazole should be reduced by approximately ½.

Example 6

Clinical Drug-Drug Interaction Study of Colchicine and Azithromycin

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there was a 14-day washout between the two periods. Twenty-four (24)

non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with the azithromycin on Day 19. Azithromycin was administered for 5 consecutive days (2×250 mg once daily [Day 15 only] and then 1×250 mg once daily Days 16-19) beginning on the morning of Day 15, with the last 250 mg azithromycin dose administered on the morning on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects were confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Azithromycin plasma concentrations were not measured.

TABLE 12

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults

	Colchicine Alone	Colchicine + Azithromycin	% Ratio
C_{max} (pg/mL), geometric mean	2535.94	2856.22	112.63
AUC_{0-t} (pg · h/mL), geometric mean	10971.51	16090.52	146.66
AUC_{∞} (pg · h/mL), geometric mean	12931.80	18312.83	141.61

TABLE 13

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Azithromycin (N = 21)	Colchicine Alone (N = 21)
AUC_{0-t} (ng · hr/mL)	17.16 (37.78)	11.98 (45.81)
$AUC_{0-\infty}$ (ng · hr/mL)	19.61 (39.15)	14.13 (46.73)
C_{max} (ng/mL)	3.05 (39.54)	2.74 (41.52)
T_{max} (hr)	1.5 (0.5-3)	1.0 (0.5-3)
$t_{1/2}$ (hr)	6.71 (68.34)[1]	6.07 (66.15)[1]
CL/F (L/hr)	35.01 (37.26)	50.24 (40.31)

Following administration of azithromycin 500 mg on Day 1 followed by 250 mg×4 days, exposure to colchicine is increased (approximately 46% for AUC_{0-t} and approximately 40% for $AUC_{0-\infty}$). Mean peak colchicine concentration increased by approximately 12% and total apparent oral clearance decreased approximately 30% with co-administration. T_{max} was not affected.

FIG. **5** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 7

Clinical Drug-Drug Interaction study of Colchicine and Diltiazem

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

As single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with diltiazem ER on Day 21. Diltiazem ER was administered for 7 consecutive days (1×240 mg capsule once daily on Days 15-21) beginning on the morning of Day 15, with the last 240 mg diltiazem ER dose administered on the morning on Day 21. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first diltiazem ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 21. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Diltiazem plasma concentrations were not measured.

TABLE 14

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults

	Colchicine Alone	Colchicine + Diltiazem	% Ratio
C_{max} (pg/mL), geometric mean	2006.42	2583.22	128.75
AUC_{0-t} (pg · h/mL), geometric mean	9154.55	15740.37	171.94
AUC_{∞} (pg · h/mL), geometric mean	11022.30	19902.98	180.57

TABLE 15

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Diltiazem (N = 20)	Colchicine Alone (N = 20)
AUC_{0-t} (ng · hr/mL)	17.73	10.04
$AUC_{0-\infty}$ (ng · hr/mL)	22.49	12.03
C_{max} (ng/mL)	2.80	2.17
T_{max} (hr)	1.48	1.15
$t_{1/2}$ (hr)	12.50	5.51
CL/F (L/hr)	463.49	395.83

FIG. **5** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 8

Clinical Drug-Drug Interaction Study of Colchicine and Verapamil

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with verapamil HCl ER on Day 19. Verapamil HCl ER was administered for 5 consecutive days (1×240 mg tablet once daily on Days 15-19) beginning on the morning of Day 15, with the last 240 mg verapamil HCl ER dose administered on the morning on Day 19. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first verapamil HCL ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects returned to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 20-23 (Period 2). Verapamil plasma concentrations were not measured.

TABLE 16

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults

	Colchicine Alone	Colchicine + Verapamil	% Ratio
C_{max} (pg/mL), geometric mean	2768.77	3639.68	131.45
AUC_{0-t} (pg · h/mL), geometric mean	12256.40	23889.21	194.94
AUC_{∞} (pg · h/mL), geometric mean	14415.79	29556.75	205.03

TABLE 17

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Verapamil (N = 24)	Colchicine Alone (N = 24)
AUC_{0-t} (ng · hr/mL)	24.64	13.09
$AUC_{0-\infty}$ (ng · hr/mL)	30.59	15.37
C_{max} (ng/mL)	3.85	2.97
T_{max} (hr)	1.15	1.22

TABLE 17-continued

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Verapamil (N = 24)	Colchicine Alone (N = 24)
$t_{1/2}$ (hr)	17.17	6.24
CL/F (L/hr)	21.01	43.93

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to").

"Concomitant" and "concomitantly" as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as one to two weeks, preferably within one to seven days, after the administration of the first drug. This is because clarithromycin can exert a long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin-administration levels for as much as two weeks after the cessation of clarithromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

A "dose" means the measured quantity of a drug to be taken at one time by a patient.

A "dosage amount" means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e. daily). A "daily dosage amount" is the total dosage amount taken in one day, that is, a 24 hour period.

"Dosing regimen" means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and

dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or different.

A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

"Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

"Risk" means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a medical treatment. An "acceptable risk" means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is "acceptable" will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An "acceptable risk" of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An "unacceptable risk" of an adverse reaction means that an individual or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. "At risk" means in a state or condition marked by a high level of risk or susceptibility.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max}, C_n, C_{24}, T_{max}, and AUC. "C_{max}" is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. "C_{min}" is the measured plasma concentration of the active agent at the point of minimum concentration. "C_n" is the measured plasma concentration of the active agent at about n hours after administration. "C_{24}" is the measured plasma concentration of the active agent at about 24 hours after administration. The term "T_{max}" refers to the time from drug administration until C_{max} is reached. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time **0** to time t, where time **0** is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-\infty}$, AUC_{∞} or AUC_{0-inf} is the calculated area under the curve of plasma concentration versus time from time **0** to time infinity. In steady-state studies, $AUC_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time **0** to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_e or K_{el}, the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{el}$. CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{∞}; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_{\infty} \times K_{el}$).

"Side effect" means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A method of treating a patient in need of treatment for acute gout flares with colchicine, comprising

orally administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil,

wherein the adjusted daily dosage amount of colchicine is 50% to 75% of an intended daily dosage amount of colchicine,

wherein the intended daily dosage amount of colchicine is a dosage amount suitable for the patient if the patient were not receiving concomitant verapamil, wherein the intended daily dosage amount of colchicine suitable for the patient if the patient were not receiving concomitant verapamil is 1.2 mg at the first sign of flare, followed by 0.6 mg one hour later, and wherein the concomitantly administered dose of verapamil is 240 mg per day.

2. The method of claim **1**, wherein the dose is not to be repeated for 3 days.

3. The method of claim **1**, wherein the adjusted daily dosage amount of colchicine is 1.2 mg.

4. The method of claim **3**, wherein the dose is not to be repeated for 3 days.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,440,721 B2
APPLICATION NO. : 13/184704
DATED : May 14, 2013
INVENTOR(S) : Matthew W. Davis

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specifications

In column 1, line 8, after "Continuation" insert -- of --.

In column 1, lines 13-14, delete "Dec. 17, 2008" and insert -- January 14, 2009 --, therefor.

In column 2, lines 22-23, delete "3-demethylchochicine" and insert -- 3-demethylcolchicine --, therefor.

In column 3, line 8, delete "in a" and insert -- in an --, therefor.

In column 3, line 51, delete "that that" and insert -- that --, therefor.

In column 4, line 42, delete "●" and insert -- ○ --, therefor.

In column 4, line 49, delete "▲" and insert -- Δ --, therefor.

In column 4, line 49, delete "●" and insert -- ○ --, therefor.

In column 4, line 50, delete "■" and insert -- □ --, therefor.

In column 4, line 56, delete "▲" and insert -- Δ --, therefor.

In column 4, line 56, delete "●" and insert -- ○ --, therefor.

In column 4, line 57, delete "■" and insert -- □ --, therefor.

In column 4, line 63, delete "▲" and insert -- Δ --, therefor.

In column 4, line 63, delete "●" and insert -- ○ --, therefor.

In column 4, line 64, delete "■" and insert -- □ --, therefor.

Signed and Sealed this
Thirteenth Day of August, 2013

Teresa Stanek Rea

Teresa Stanek Rea
Acting Director of the United States Patent and Trademark Office

In column 6, line 48, delete "in a" and insert -- in --, therefor.

In column 8, line 56, after "may" insert -- be --.

In column 8, line 59, delete "wherein the" and insert -- the --, therefor.

In column 9, line 2, after "amount" insert -- is --.

In column 9, line 29, after "may" insert -- be --.

In column 9, line 32, delete "wherein the" and insert -- the --, therefor.

In column 9, line 41, after "amount" insert -- is --.

In column 9, line 67, after "may" insert -- be --.

In column 10, line 3, delete "wherein the" and insert -- the --, therefor.

In column 10, line 13, after "amount" insert -- is --.

In column 10, line 51, after "may" insert -- be --.

In column 10, line 60, after "amount" insert -- is --.

In column 12, line 4, delete "amount of" and insert -- amount for --, therefor.

In column 12, line 17, before "Colchicine" insert -- Table 2 --.

In column 13, line 23, delete "levels[1]" and insert -- levels --, therefor.

In column 13, line 40, delete "levels[1]" and insert -- levels --, therefor.

In column 15, line 30, delete "9" and insert -- 9, --, therefor.

In column 16, line 13, delete "9" and insert -- 9, --, therefor.

In column 16, line 66, delete "the administering" and insert -- administering --, therefor.

In column 18, line 27, delete "are" and insert -- were --, therefor.

In column 18, line 37, delete "3-O-demethylcolchciine" and insert
-- 3-O-demethylcolchicine --, therefor.

In column 18, line 53, delete "Cmin" and insert -- C_{min} --, therefor.

In column 18, line 54, delete "Cmin" and insert -- C_{min} --, therefor.

In column 18, line 55, delete "Cmin" and insert -- C_{min} --, therefor.

In column 18, line 57, delete "Cmin" and insert -- C_{min} --, therefor.

In column 18, line 62, delete "Cmax" and insert -- C_{max} --, therefor.

In column 18, line 63, delete "AUC∞" and insert -- AUC_{∞} --, therefor.

In column 19, line 10, delete "Cmax" and insert -- C_{max} --, therefor.

In column 19, line 12, delete "Tmax" and insert -- T_{max} --, therefor.

In column 19, line 48, delete "Vd/F" and insert -- V_d/F --, therefor.

In column 19, line 59, delete "Vd = CL/Ke" and insert -- $V_d = CL/K_e$ --, therefor.

In column 19, line 63, delete "AUC0-$_{tau}$;" and insert -- $AUC_{0\text{-}tau}$; --, therefor.

In column 20, line 54, delete "Pgp" and insert -- P-gp --, therefor.

In column 20, line 62, delete "(VA)" and insert -- ($t_{1/2}$) --, therefor.

In column 20, lines 66-67, after "below" delete "and illustrated in Table 5".

In column 21, line 13, after "T_{max} (hr)" delete "*".

In column 21, lines 48-49, delete "were then return" and insert -- then returned --, therefor.

In column 21, line 60, after "Arithmetic Mean" delete "(% CV)".

In column 22, line 7, after "Arithmetic Mean" delete "(% CV)".

In column 22, line 12, after "T_{max} (hr)" delete "*".

In column 22, line 33, delete "will be" and insert -- was --, therefor.

In column 23, line 4, delete "Ritonovir" and insert -- Ritonavir --, therefor.

In column 23, line 7, delete "Ritonovir" and insert -- Ritonavir --, therefor.

In column 23, line 55, delete "will be" and insert -- was --, therefor.

In column 23, lines 65-66, delete "will be" and insert -- were --, therefor.

In column 24, line 7, delete "returnee" and insert -- returned --, therefor.

In column 24, line 32, after "Arithmetic Mean" delete "(% CV)".

In column 24, line 42, after "*Median" delete "(Range)".

In column 25, line 56, delete "(68.34)[1]" and insert -- (68.34) --, therefor.

In column 25, line 56, delete "(66.15)[1]" and insert -- (66.15) --, therefor.

In column 26, line 16, delete "As" and insert -- A --, therefor.

In column 26, line 56, after "Arithmetic Mean" delete "(% CV)".

In column 26, line 57, after "Median" delete "(Range)".

In column 27, line 58, after "Arithmetic Mean" delete "(% CV)".

In column 28, line 59, after "Median" delete "(Range)".

EXHIBIT Q

US008440722B2

(12) **United States Patent**
Davis

(10) **Patent No.: US 8,440,722 B2**
(45) **Date of Patent: *May 14, 2013**

(54) **METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT**

(75) Inventor: **Matthew W. Davis**, Erwinna, PA (US)

(73) Assignee: **Takeda Pharamceuticals U.S.A., Inc.**, Deerfield, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/454,255**

(22) Filed: **Apr. 24, 2012**

(65) **Prior Publication Data**

US 2012/0208891 A1 Aug. 16, 2012

Related U.S. Application Data

(60) Division of application No. 13/184,704, filed on Jul. 18, 2011, which is a continuation of application No. 12/909,171, filed on Oct. 21, 2010, now abandoned, which is a continuation of application No. 12/372,046, filed on Feb. 17, 2009, now Pat. No. 7,820,681.

(60) Provisional application No. 61/138,141, filed on Jan. 14, 2009, provisional application No. 61/152,067, filed on Feb. 12, 2009.

(51) **Int. Cl.**

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C07C 207/00	(2006.01)

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USPC **514/629**; 564/123; 564/308; 564/427; 568/306

(58) **Field of Classification Search** ... 514/629; 564/123, 564/308, 427; 568/306
See application file for complete search history.

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(57) **ABSTRACT**

Methods for concomitant administration of colchicine together with one or more second active agents, e.g., verapamil, are disclosed. Such methods reduce the dangers commonly associated with such concomitant administration and provide additional benefits. Methods of notifying health care practitioners and patients regarding appropriate dosing for concomitant administration of colchicine together with second active agents are also provided.

2 Claims, 5 Drawing Sheets

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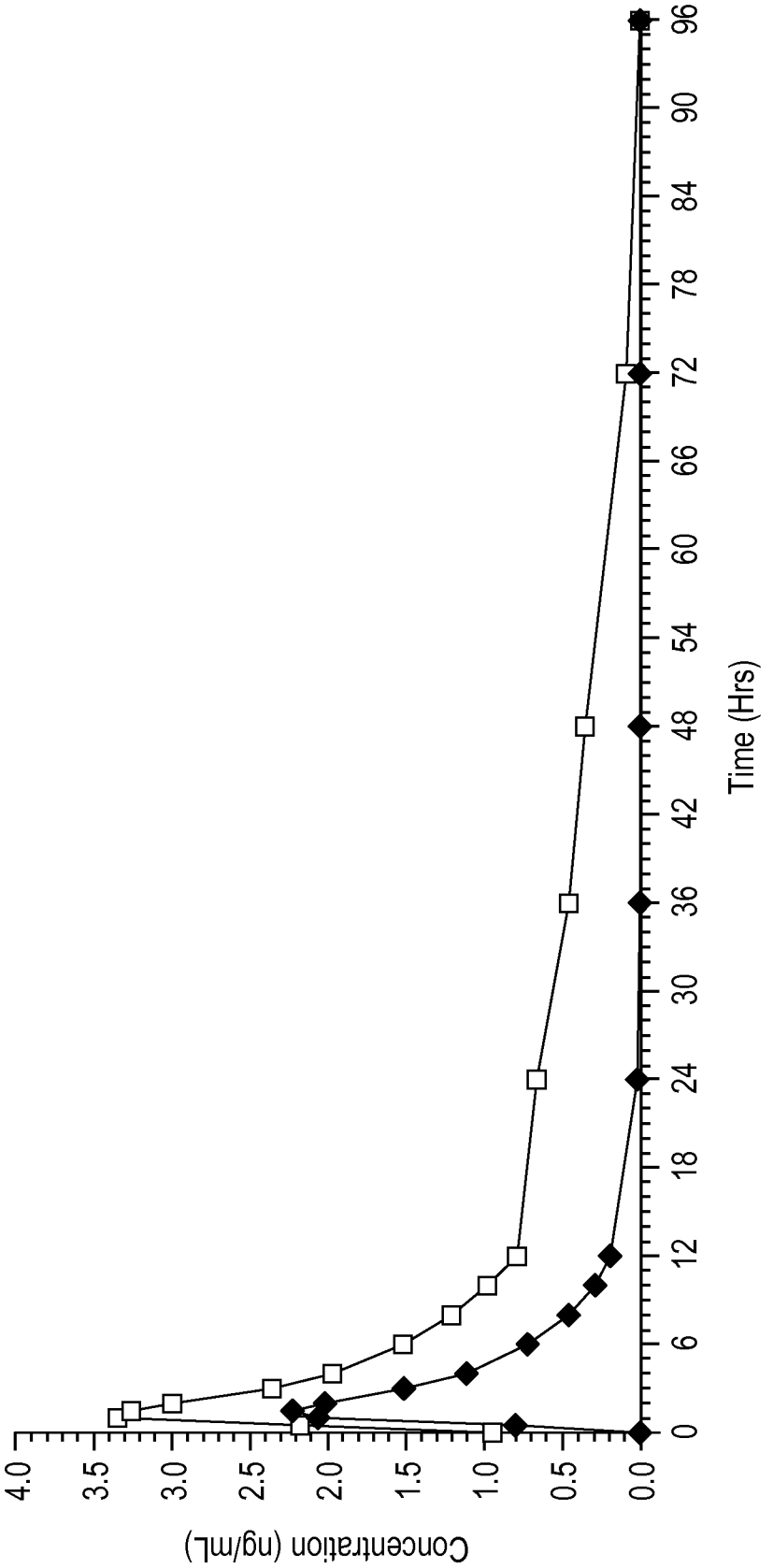
FIG. 1


Concentration (ng/mL)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Time (Hrs)
0
6
12
18
24
30
36
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48
54
60
66
72
78
84
90
96

FIG. 2

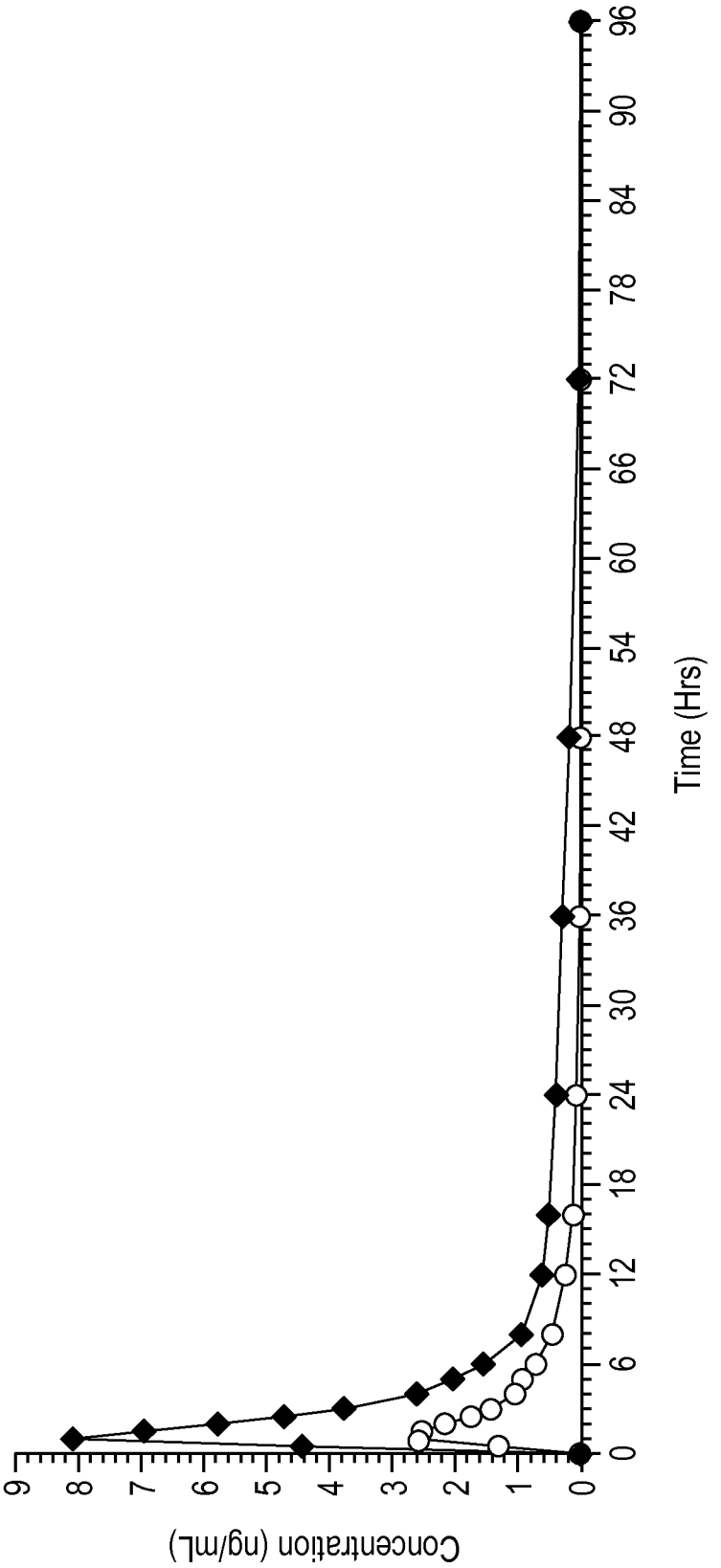

Concentration (ng/mL)
0
1
2
3
4
5
6
7
8
9
Time (Hrs)
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
90
96

FIG. 3

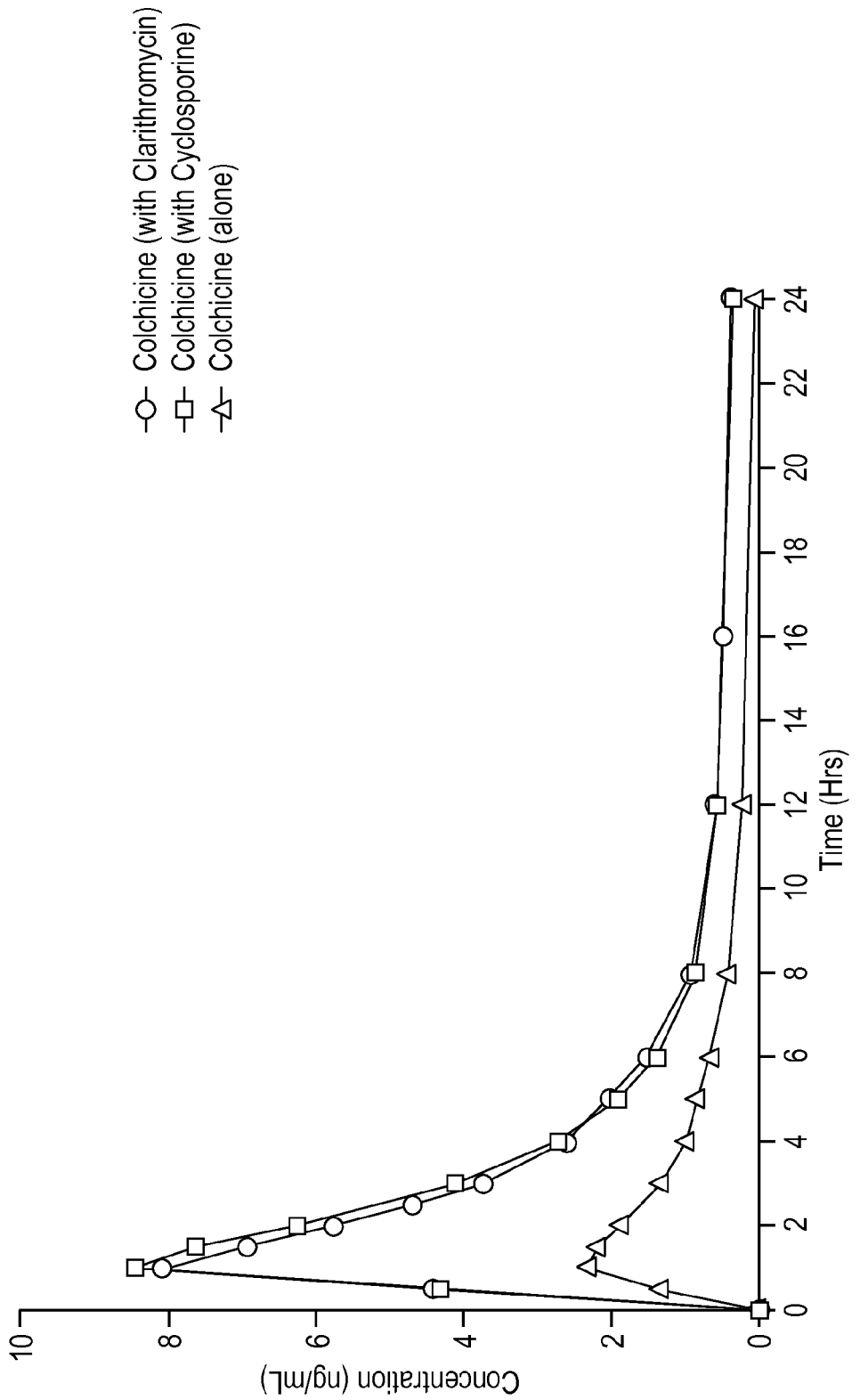

Colchicine (with Clarithromycin)
Colchicine (with Cyclosporine)
Colchicine (alone)
Concentration (ng/mL)
0
2
4
6
8
10
Time (Hrs)
0
2
4
6
8
10
12
14
16
18
20
22
24

FIG. 4

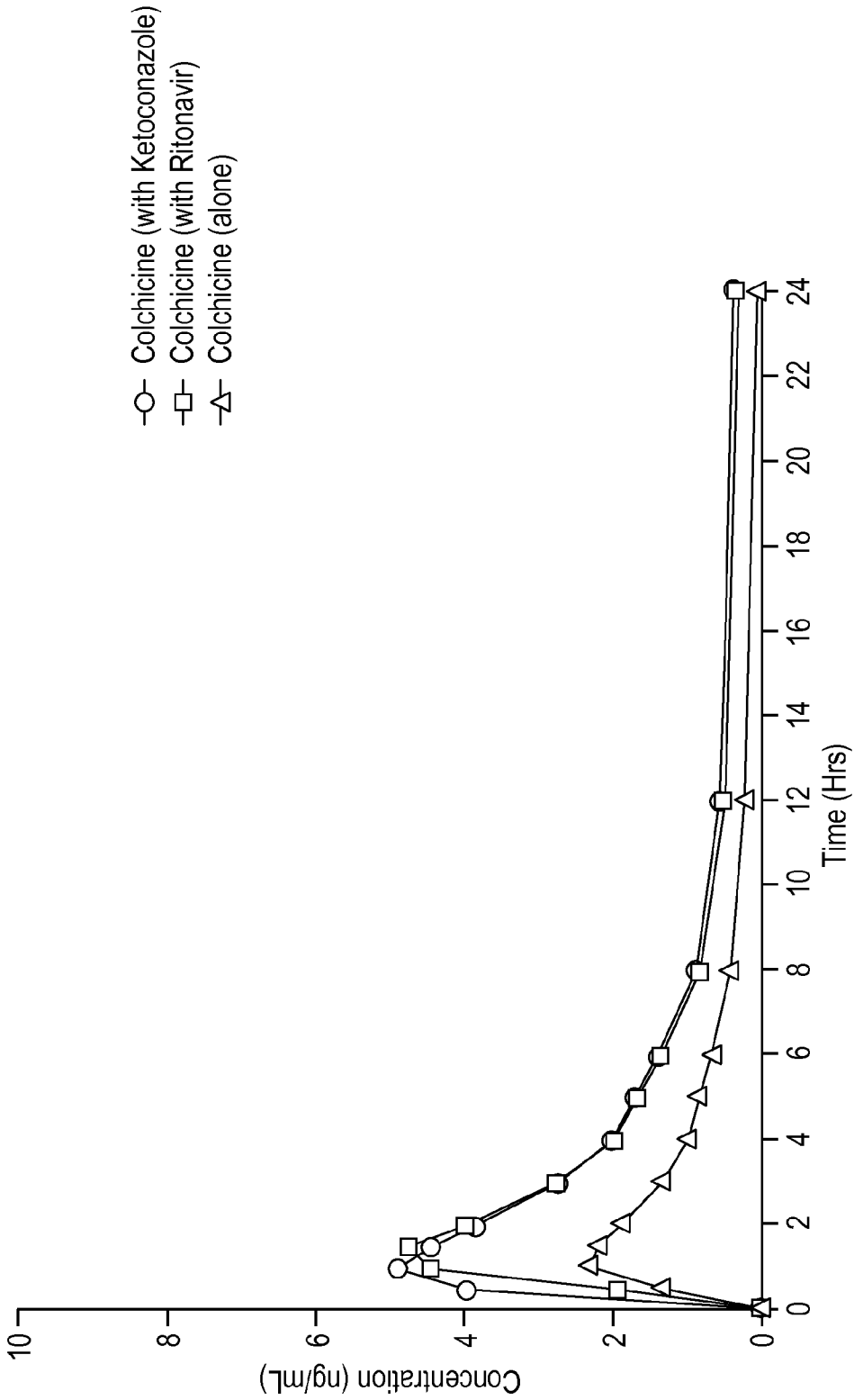
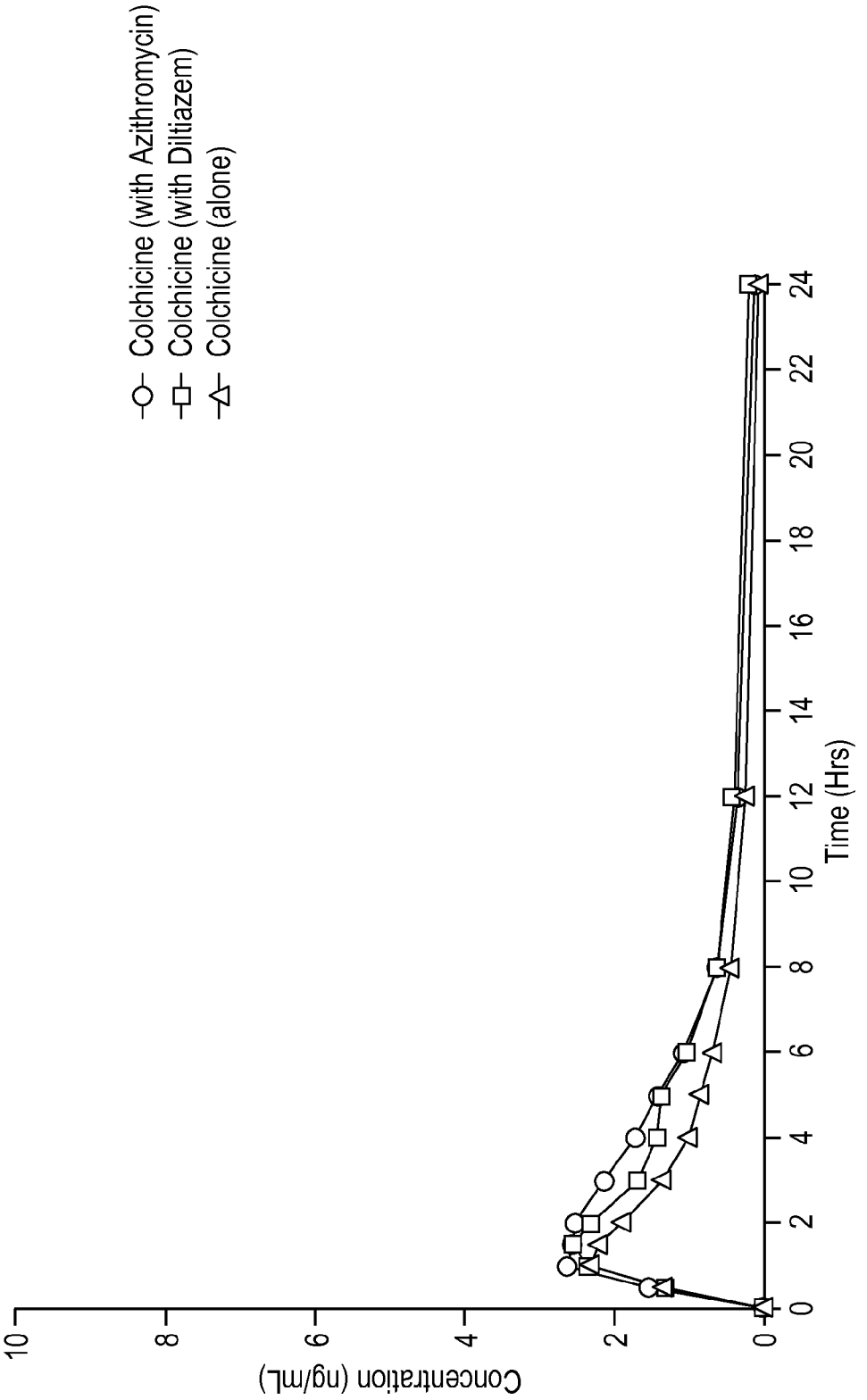

Colchicine (with Ketoconazole)
Colchicine (with Ritonavir)
Colchicine (alone)
Concentration (ng/mL)
Time (Hrs)
0
2
4
6
8
10
0
2
4
6
8
10
12
14
16
18
20
22
24

FIG. 5


Colchicine (with Azithromycin)
Colchicine (with Diltiazem)
Colchicine (alone)
Concentration (ng/mL)
0
2
4
6
8
10
Time (Hrs)
0
2
4
6
8
10
12
14
16
18
20
22
24

METHODS FOR CONCOMITANT ADMINISTRATION OF COLCHICINE AND A SECOND ACTIVE AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Divisional of U.S. application Ser. No. 13/184,704 filed on Jul. 18, 2011, which is a Continuation U.S. application Ser. No. 12/909,171, filed Oct. 21, 2010, which is a continuation of U.S. application Ser. No. 12/372,046, filed Feb. 17, 2009, now U.S. Pat. No. 7,820,681, issued Oct. 26, 2010, which claims priority from U.S. Provisional Application Ser. Nos. 61/138,141 filed Dec. 17, 2008 and 61/152,067 filed Feb. 12, 2009, all of which are hereby incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

This disclosure relates to methods allowing for the co-administration of colchicine together with one or more second active agents for therapeutic purposes with improved safety compared to prior methods of administration.

BACKGROUND

Colchicine, chemical name (−)-N-[(7S,12a5)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]-acetamide, is an alkaloid found in extracts of *Colchicum autumnale, Gloriosa superba*, and other plants. It is a microtubule-disrupting agent used in the treatment of gout and other conditions that may be treated, relieved or prevented with anti-inflammatory treatment. Colchicine impairs the motility of granulocytes and can prevent the inflammatory phenomena that initiate an attack (or flare) of gout. Colchicine also inhibits mitosis, resulting in effects in cells with high turnover rates such as those in the gastrointestinal tract and bone marrow. The primary adverse side effects of colchicine therapy include gastrointestinal upset such as diarrhea and nausea.

Colchicine has a narrow therapeutic index. The margin between an effective dose and a toxic dose of colchicine is much narrower than that of many other widely used drugs. Consequently, actions that result in increased colchicine levels in patients receiving colchicine therapy are particularly dangerous. Co-administration of colchicine to patients along with certain other drugs can have the effect of increasing colchicine levels. Such drug-drug interactions with colchicine have been reported to result in serious morbid complications and, in some cases, death.

Colchicine is rapidly absorbed from the gastrointestinal tract. Peak concentrations occur in 0.5 to 2 hours. The drug and its metabolites are distributed in leukocytes, kidneys, liver, spleen and the intestinal tract. Colchicine is metabolized in the liver and excreted primarily in the feces with 10 to 20% eliminated unchanged in the urine.

Gout (or gouty arthritis) is a disease caused by a build up of uric acid in the joints. Such a build up is typically due to an overproduction of uric acid, or to a reduced ability of the kidney to excrete uric acid. Gout is characterized by excruciating, sudden, unexpected, burning pain, as well as by swelling, redness, warmness, and stiffness in the affected joint. Low-grade fever may also be present. A gout flare is a sudden attack of pain in affected joints, especially in the lower extremities, and most commonly in the big toe. In afflicted individuals, the frequency of gout flares typically increases over time. In this manner, gout progresses from acute gout to chronic gout, which involves repeated episodes of joint pain.

Colchicine can reduce pain in attacks of acute gout flares and also can be used beneficially for treating adults for prophylaxis of gout flares. Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and subsequent inflammatory responses.

Cytochrome p450 (CYP) enzymes are agents of drug metabolism that are found in the liver, the gastrointestinal tract and other locations in the body. CYP enzymes occur in a variety of closely related proteins referred to as isozymes and different CYP isozymes may preferentially metabolize different drugs. The 3A family of CYP isozymes, particularly CYP3A4, is also known to be involved in many clinically significant drug-drug interactions, including those involving colchicine and second active agents. While drugs are often targets of CYP-mediated metabolism, some may also alter the expression and activity of such enzymes, thus impacting the metabolism of other drugs. The biotransformation of colchicine in human liver microsomes involves formation of 3-demethylcolchicine and 2-demethylcolchicine. As shown by experiments using antibodies against CYP3A4 and experiments using chemical inhibition of CYP3A4, this transformation is correlated with (and thus apparently mediated by) CYP3A4 activity.

P-glycoprotein (P-gp) is an ATP-dependent cell surface transporter molecule that acts as an ATPase efflux pump for multiple cytotoxic agents, including colchicine. P-gp actively pumps certain compounds, including drugs such as colchicine, out of cells. P-gp is encoded by the Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene, also referred to as the multiple drug resistance 1 gene (MDR1).

Since colchicine acts intracellularly, the combined effects of CYP3A4 inhibition and P-gp inhibition by second active agents that also interact with CYP3A4 and P-gp can cause colchicine toxicity in patients taking what would be a safe dose of colchicine in the absence of concomitant second agent administration. Various studies of adverse reactions from exposure to multiple drugs have found that 6.5-23% of the adverse reactions result from drug-drug interactions. Unfortunately, each year a number of deaths occur as the direct result of patients adding a concomitant prescription pharmaceutical product to their existing medication regimen.

There accordingly remains a need for improved methods for administering colchicine to individuals who are concomitantly being treated with second active agents so as to reduce the possibility of colchicine toxicity while maintaining the sometimes life-saving advantages of being able to administer the two (or more) agents concomitantly. The present disclosure addresses this need and provides further advantages.

SUMMARY

In one embodiment, a method of treating an individual in need of treatment with colchicine comprises concomitantly administering to the individual colchicine and another drug, for example, ketoconazole or ritonavir or cyclosporine, wherein the colchicine is administered as a dosing regimen with a starting colchicine dose of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently

than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg. According to another embodiment, the other drug is, for example, verapamil or diltiazem, and the starting colchicine dose during coadministration with the other drug is no more than about 1.2 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours.

In another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in an individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-t} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max}, AUC_{0-t}, AUC_{0-inf}, or clearance in a matched individual not administered concomitant ketoconazole.

In yet another aspect, a method of using colchicine comprises increasing the blood plasma levels of colchicine in an individual being administered doses of about 0.6 mg or less of colchicine to treat a colchicine-treatable condition, said method comprising the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-t} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max}, AUC_{0-t}, or clearance in a matched individual not administered concomitant ritonavir.

In another embodiment, a method for using colchicine comprises a pharmacy receiving a prescription for colchicine for a patient who is concomitantly being treated with ketoconazole or ritonavir or verapamil, and the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by: entering, into a first computer readable storage medium in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient, wherein the computer has been programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that ketoconazole or ritonavir or verapamil is being concomitantly administered to the patient, wherein, upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that that ketoconazole or ritonavir is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than about 0.6 mg colchicine, followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour wherein each additional colchicine dose is no greater than about 0.6 mg.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a dose suitable for the patient if the patient were not receiving concomitant ritonavir.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is about 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole.

A method of treating an individual in need of treatment for gout flares, comprises concomitantly administering colchicine and azithromycin, and carefully monitoring the individual for potential toxicity. The method further comprises adjusting the dose of colchicine or azithromycin as necessary to avoid adverse side effects.

A method of treating an individual with colchicine comprises concomitantly administering colchicine and verapamil, and carefully monitoring the individual for signs and symptoms of adverse side effects. The method further comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is about 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for a patient if the patient were not receiving concomitant verapamil.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults, N=13, Y axis=colchicine concentration, ng/mL, X axis=time in hours, ♦=day 1, □=day 25. See Example 1.

FIG. **2** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults, Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=23, ●=colchicine alone, ♦=colchicine plus clarithromycin. See Example 2.

FIG. **3** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus clarithromycin, ■=colchicine plus cyclosporine.

FIG. **4** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ketoconazole and steady-state ritonavir in healthy adults. Y axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus ketoconazole, ■=colchicine plus ritonavir.

FIG. **5** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults. Y

axis=colchicine concentration, ng/mL, X axis=time in hours, N=18, ▲=colchicine alone, ●=colchicine plus azithromycin, ■=colchicine plus diltiazem.

These and other embodiments, advantages and features of the present invention become clear when detailed description is provided in subsequent sections.

DETAILED DESCRIPTION

Disclosed herein are methods for safely administering colchicine concomitantly with a second active agent, wherein the second active agent is a CYP3A4 inhibitor, a P-gp inhibitor, or both. Exemplary second active agents that are CYP3A4 and P-gp inhibitors are azithromycin, ketoconazole, ritonavir, diltiazem, verapamil and cyclosporine. It has now been discovered that certain reduced or limited colchicine dosage amounts, when administered with concomitantly administered recommended dosage amounts of second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, achieve plasma colchicine levels that are therapeutically effective, but are not significantly higher, and therefore not significantly more toxic, than plasma levels achieved by administration of manufacturers' recommended colchicine dosages in the absence of concomitant administration with the second active agent. Thus, colchicine and second active agents that are CYP3A4 inhibitors, P-gp inhibitors, or both, can be administered concomitantly with improved safety when colchicine is administered as disclosed herein.

Without being held to theory, it has been hypothesized by the inventors herein that P-gp inhibition is more important in the elimination of colchicine than CYP3A4 inhibition. The CYP3A4 and P-gp inhibition potential of clarithromycin, azithromycin, ketoconazole, ritonavir, diltiazem and cyclosporine are given in Table 1. Based on their level of P-gp inhibition, it was predicted that clarithromycin and cyclosporine will increase colchicine concentrations more than ketoconazole or ritonavir, which will increase colchicine levels more than verapamil, azithromycin or diltiazem. The results presented herein confirm this hypothesis.

TABLE 1

CYP3A4 and P-gp inhibition potential of second active agents

Drug	CYP3A Inhibition potential	P-gp Inhibition potential
Clarithromycin	+++++	+++++
Cyclosporine	+++++	+++++
Ketoconazole	+++++	+++
Ritonavir	+++++	+++
Verapamil	++	++
Diltiazem	+	+
Azithromycin	+	+

Ritonavir (Norvir®, Abbott Laboratories) is an inhibitor of Human Immunodeficiency Virus (HIV) protease and is approved for the treatment of HIV-infection when used as part of a highly active antiretroviral therapy (HAART) regimen at the recommended dose of 600 mg twice daily. Although a very potent and effective protease inhibitor at the recommended dose, ritonavir is not well tolerated by HIV-infected patients at the approved dose and therefore, is generally not used clinically as a sole, therapeutic protease inhibitor within a HAART regimen. Rather, ritonavir is used more often as a pharmacokinetic enhancer or 'boosting agent' when combined with other approved protease inhibitors that are CYP3A4 and P-gp substrates and also have inherent bioavailability issues, such as poor bioavailability due to first pass effect. Improving the pharmacokinetic disposition of other protease inhibitors is possible due to the potent CYP3A4 and P-gp inhibitory activity ritonavir possesses. Sub-therapeutic ritonavir doses are used to achieve pharmacokinetic enhancement of the co-administered protease inhibitors; typically 100 mg of ritonavir administered twice daily is the ritonavir dose used in combination with the primary protease inhibitor. This low-dose ritonavir regimen boosts the bioavailability of the second protease inhibitor without contributing significantly to the adverse event profile of the HAART regimen.

Cyclosporine (Neoral®, Novartis Pharmaceuticals Corporation) is the active principle in Neoral® an oral formulation that immediately forms a microemulsion in an aqueous environment. Cyclosporine is indicated for kidney, liver, and heart transplantation; rheumatoid arthritis and psoriasis. Cyclosporine is extensively metabolized by the CYP3A4 enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents.

Ketoconazole is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole is a potent inhibitor of the CYP3A4 enzyme system. Co-administration of ketoconazole and drugs primarily metabolized by the CYP3A4 enzyme may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse side effects.

Azithromycin is a macrolide antibiotic indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in specific conditions. Azithromycin remains the sole agent developed and marketed within the azalide macrolide subclass. Due to its dibasic structure, azithromycin has demonstrated unique pharmacokinetic properties that differ significantly from those of classic macrolide agents. Azithromycin's pharmacokinetics are characterized by low concentrations in serum, secondary to rapid and significant uptake by fibroblasts and acute reactant cells such as polymorphonuclear leukocytes (PMNs), monocytes, and lymphocytes. Azithromycin is a weak to moderate CYP3A4 inhibitor.

Diltiazem (Cardizem® CD, Biovail Pharmaceuticals, Inc. [Biovail]) is an extended-release (ER) calcium ion influx inhibitor available in blue capsules, each containing 240 mg diltiazem hydrochloride for oral administration. Diltiazem ER capsules are indicated for the treatment of hypertension and the management of chronic stable angina and angina due to coronary artery spasm. Diltiazem is a CYP3A4 and P-gp inhibitor.

Verapamil HCl ER (Mylan Pharmaceuticals, Inc.) is a calcium ion influx inhibitor available in a pale green, capsule shaped, film-coated tablets, each containing 240 mg verapamil hydrochloride for oral administration. Verapamil HCl ER tablets are indicated for the management of hypertension. Verapamil HCl ER is a potent CYP3A4 and P-gp inhibitor.

In one embodiment, colchicine is administered to an individual suffering from a condition treatable with colchicine, and the concomitant second active agent (e.g., ketoconazole, ritonavir, cyclosporine, verapamil, or diltiazem or any other CYP3A4 or P-gp inhibitor) is administered concurrently while the colchicine administration is reduced, or the individual has recently completed a dosing regimen of the second

active agent, in which case the colchicine administration may still be reduced for a period of time.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., ketoconazole, ritonavir, or cyclosporine) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 0.6 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or about 0.3 mg, and each additional colchicine dose is about 0.3 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 0.6 mg, and each additional colchicine dose, if any, is about 0.3 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, disclosed herein is a method of administering colchicine and a second active agent (e.g., verapamil or diltiazem) wherein an individual is administered the colchicine according to a colchicine dosing regimen of a single starting colchicine dose of no more than about 1.2 mg colchicine, followed by either no additional colchicine doses within about 12, 24, 48, or 72 hours, or followed by at least one additional colchicine dose within 12 hours and no more frequently than once every hour (e.g., every 3, 4, 6, 8, or 12 hours). In this embodiment, each additional colchicine dose is specifically no greater than about 0.3 mg or 0.6 mg and the individual is an adult individual or a pediatric individual. Specifically, the starting colchicine dose is about 0.6 mg or 1.2 mg, and each additional colchicine dose is about 0.3 mg or 0.6 mg. In one embodiment, when additional doses are administered, only two, three, or four additional colchicine doses are administered within about 24 hours. Specifically, the individual is an adult individual and the starting colchicine dose is about 1.2 mg, and each additional colchicine dose, if any, is about 0.3 mg or 0.6 mg. In one embodiment, only three additional colchicine doses are administered within about 24 hours.

In one embodiment, the second active agent is ketoconazole or ritonavir. In one embodiment, the ketoconazole is administered to the individual at a dosage of about 200 mg daily and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the ritonavir is administered to the individual at a dosage of about 200 to 1200 mg daily (e.g., in 2×100 mg doses or 2×600 mg doses) and the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by 0, 1, 2, 3, or 4 additional colchicine doses of about 0.6 mg every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In an exemplary regimen for treatment of acute gout flares, ingestion of colchicine is continued until a total of no more than about 1.2, 1.4, 1.6, 1.8, 2, or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is stopped until a subsequent acute gout flare occurs. More preferably, the colchicine is administered as a dosage form of 0.6 mg (e.g., one 0.6 mg colchicine tablet), or 0.3 mg (e.g., one half of a 0.6 mg tablet) of colchicine and administration of the dosage form is not repeated within a period of at least about two days, preferably at least about three days.

In one embodiment, the second active agent (e.g., ketoconazole or ritonavir or cyclosporine) is administered to the individual before the colchicine is administered to the individual, and wherein the administration of second active agent is terminated no more than about fourteen days prior to the initiation of colchicine administration. For example, the method comprises administering colchicine to an individual also taking a second active agent (e.g., ketoconazole or ritonavir or cyclosporine), or having completed treatment with the second active agent within the prior 14 days, the individual being administered a single dose of about 0.6 mg or about 0.3 mg of colchicine to treat a gout flare, which administration is not repeated within any 3-day period. According to this embodiment if the second active agent is instead verapamil or diltiazem, if the second active agent is terminated no more than about fourteen days prior to the initiation of the colchicine administration to treat a gout flare, the single dose of colchicine is about 1.2 mg not to be repeated within a 3-day period.

In another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ketoconazole to increase the C_{max} of colchicine by about 90%, or to increase the AUC_{0-t} of colchicine in the individual by about 190%, or to increase the AUC_{0-inf} of colchicine in the individual by about 205%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max}, AUC_{0-t}, or clearance in the same or a matched individual when not being administered a concomitant ketoconazole. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ketoconazole is about 200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In yet another aspect, herein disclosed is a method for increasing the blood plasma levels of colchicine in an individual to whom colchicine is being administered to treat or prevent a colchicine-responsive condition. This method comprises the concomitant dosing of the individual with a sufficient amount of ritonavir to increase the C_{max} of colchicine by about 170%, or to increase the AUC_{0-t} of colchicine in the individual by about 245%, or to decrease the clearance of colchicine by about 70%, compared to the C_{max}, AUC_{0-t}, or clearance in the same or a matched individual when not being administered concomitant ritonavir. In a specific embodiment, the individual is being administered no more than hourly doses of about 0.6 mg of colchicine or less, and the amount of ritonavir is about 200 to about 1200 mg. In one embodiment, the single dose is one 0.6 mg colchicine tablet.

In one embodiment, a method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ritonavir, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ritonavir. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduce from a 0.6 mg twice daily intended dose to a 0.6 mg

once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ritonavir is, for example, 200 mg per day. In one embodiment, the ritonavir is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ritonavir is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of ketoconazole, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant ketoconazole. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduce from a 0.6 mg twice daily intended dose to a 0.6 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of ketoconazole is, for example, 250 mg per day. In one embodiment, the ketoconazole is administered to the patient before the colchicine is administered to the patient, and wherein the administration of ketoconazole is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of cyclosporine, wherein the adjusted daily dosage amount of colchicine is 25% to 50% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant cyclosporine. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduce from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted dose. Alternatively, when the colchicine is administered to prevent gout flares, wherein the adjusted daily dosage amount of colchicine is reduced from a 0.6 mg once daily intended dose to a 0.3 mg once every other day adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 0.6 mg, not to be repeated within 3 days. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is 0.6 to 1.2 mg, not to be repeated within 3 days. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. In another embodiment, treating is for familial Mediterranean fever and the intended daily dosage amount is 0.9 to 1.8 mg for children 6-12 years or 4-6 years, and the maximum adjusted daily dosage amount is 0.6 mg, given, for example, in two 0.3 mg doses. The concomitantly administered dose of cyclosporine can be various dosage strengths administered per day, and can be administered as an oral preparation, topically, or intravenously. In one embodiment, the cyclosporine is administered to the patient before the colchicine is administered to the patient, and wherein the administration of cyclosporine is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

In another embodiment, colchicine is concomitantly administered with azithromycin. Concomitant administration of azithromycin with colchicine increases exposure to colchicine approximately 46% and thus has the potential to produce colchicine toxicity. During concomitant use of azithromycin and colchicine, the physician should carefully monitor individuals for any signs or symptoms of colchicine toxicity. Additionally, dosing adjustments to either the colchicine and/or the azithromycin may be necessary to avoid adverse side effects.

A method of treating a patient with colchicine comprises administering an adjusted daily dosage amount of colchicine

to the patient who is receiving concomitant administration of verapamil, wherein the adjusted daily dosage amount of colchicine is 50% to 75% of an intended daily dosage amount of colchicine, and wherein the intended daily dosage amount of colchicine is a daily dosage amount suitable for the patient if the patient were not receiving concomitant verapamil. Treating is, for example, to prevent gout flares, to treat acute gout, or to treat familial Mediterranean fever. When the colchicine is administered to prevent gout flares, the adjusted daily dosage amount of colchicine may reduce from a 0.6 mg twice daily intended dose to a 0.3 mg once daily adjusted dose. In one embodiment, when treating is for acute gout, the intended daily dosage amount is 1.8 to 2.4 mg, and the maximum adjusted daily dosage amount is 1.2 mg. In another embodiment, treating is for acute gout, the intended daily dosage amount is 2.4 to 4.8 mg and the maximum adjusted daily dosage amount is about one-third the intended daily dosage amount. In yet another embodiment, treating is for familial Mediterranean fever and the daily dosage amount 1.2 to 2.4 mg for adults, and the maximum adjusted daily dosage amount is 1.2 mg, given, for example, in two 0.6 mg doses. In one embodiment, the verapamil is administered to the patient before the colchicine is administered to the patient, and wherein the administration of verapamil is terminated no more than about fourteen days prior to the initiation of colchicine administration. The method optionally further comprises carefully monitoring the individual for potential toxicity. Any 0.3 mg dose contemplated in this method can be a single 0.3 mg dosage form or one-half a 0.6 mg dosage form, e.g. one-half a 0.6 mg colchicine tablet.

Disclosed herein are specific dosage reductions of colchicine that improve safety when colchicine is co-administered with certain active agents. The dose of colchicine recommended for administration without co-administration of certain other active agents, such as CYP3A4 or P-gp inhibitors, is referred to as an intended daily dosage amount. The reduced or modified daily dosage amount determined from the experiments presented herein is referred to as an adjusted daily dosage amount. An adjusted daily dosage amount is thus a daily dosage amount that can be safely co-administered with a second active agent as disclosed herein. A dose adjustment is thus a dose of colchicine and does not include cessation of colchicine, that is, a dose of 0 mg of colchicine.

In these and other embodiments, the colchicine-responsive condition is gout (e.g., a gout flare in a chronic gout sufferer), familial Mediterranean fever (FMF), thrombocytopenic purpura, pericarditis, scleroderma, or Behçet's disease. In some embodiments, the treatment with colchicine is either palliative or prophylactic. The gout may be acute gout, e.g. a gout flare, or chronic gout.

Acute Gout

Acute gout, or gout flares, can be treated according to the following treatment schedule. This table indicates the original, or intended, dose, i.e., the dose of colchicine recommended absent concomitant administration of the drugs listed below. This table also presents the dose adjustment of the present invention, or the recommended colchicine dose to be administered when the strong and moderate CYP3A4 and P-gp inhibitors are administered concomitantly with colchicine when the patient is being treated for acute gout, or an acute gout flare.

	Colchicine Dose Recommendation	
Drug	Original Intended Dose (Total Dose)	Dose Adjustment
Strong CYP3A4 Inhibitors	Regimen Reduced by Two Thirds	
Erythromycin Ketoconazole Ritonavir	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days.
Moderate CYP3A4 Inhibitors	Regimen Reduced by One Third	
Diltiazem Verapamil	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days.	1.2 mg (2 tablets) × 1 dose. Dose to be repeated no earlier than 3 days.
Strong P-gp Inhibitors	Regimen Reduced by Two Thirds	
Cyclosporine	1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Dose to be repeated no earlier than 3 days.	0.6 mg (1 tablet) × 1 dose. Dose to be repeated no earlier than 3 days.

Chronic Gout

For chronic gout, an original intended daily dosage amount is 1.2 mg or 6 mg. Alternatively, an intended daily dosage amount of chronic gout can be as much as 2.4 mg per day. The daily dosage amount for chronic gout can be administered at one time or dosed at intervals throughout the day, e.g. twice daily, three times daily, or four times daily.

Chronic gout, with and without a concomitant dose of another drug, can be treated according to the following treatment schedule:

Colchicine Dose Adjustment for Co-Administration with Interacting Drugs if No Alternative Available

	Colchicine Dose Recommendation	
Drug	Original Intended Dose	Dose Adjustment
Clarithromycin	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Cyclosporine	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Erythromycin	0.6 mg twice daily	0.3 mg once daily
	0.6 mg once daily	0.3 mg once every other day
Ritonavir	0.6 mg twice daily	0.6 mg once daily
	0.6 mg once daily	0.3 mg once daily

Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) can be treated according to the following intended daily dosing schedule:

	Daily dosage amount	
Age	Usual	Maximum
Adults and children >12 years	1.2 mg	2.4 mg
Children >6 to 12 years	0.9 mg	1.8 mg
Children 4 to 6 years	0.3 mg	1.8 mg

When colchicine is given to patients with FMF concomitantly with other drugs, the adjusted (reduced) dosage amount of colchicine, according to this embodiment, is provided in the table below:

Concomitant Drug Class or Food	Noted or Anticipated Outcome	Clinical Comment
Strong CYP3A4 Inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	Significant increase in colchicine plasma levels[1]; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated.
Moderate CYP3A4 inhibitors: amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil	Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	Use colchicine with caution at reduced maximum dose of 0.6 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use a maximum dose of 0.3 mg twice daily.
Strong P-gp Inhibitors e.g. Cyclosporine, ranolazine.	Significant increase in colchicine plasma levels[1]; fatal colchicine toxicity has been reported with cyclosporine, a strong P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong P-gp inhibitors.	Use colchicine with caution at reduced maximum dose of 0.3 mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated.

Pharmacy management systems are computer-based systems that are widely used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to individuals. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067,524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Many pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In another aspect, herein disclosed are methods for using colchicine which methods involve the use of pharmacy management systems.

In one aspect, one such method comprises a pharmacy receiving a prescription for colchicine for a patient who is suffering from gout (e.g., acute gout flares or chronic gout) and who is concomitantly being treated with a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A and P-glycoprotein, followed by the pharmacy dispensing colchicine in response to receipt of the prescription, wherein the dispensing is preceded by entry into a first computer readable storage medium, in functional communication with a computer, of a unique patient identifier for said patient and at least one drug identifier for colchicine linked to the patient identifier so as to indicate that colchicine is to be administered to the patient. The computer is programmed to issue a drug-drug interaction alert when the at least one drug identifier for colchicine is entered linked to the patient identifier so as to indicate that colchicine is to be administered to the patient and when the patient identifier is also linked to an identifier indicating that a second active agent (e.g., ketoconazole or ritonavir) that is an inhibitor of CYP3A4 or P-glycoprotein is being concomitantly administered to the patient. Upon entry of the at least one drug identifier for colchicine linked to the patient identifier, a drug-drug interaction alert is issued to one or more of a pharmacy technician, a pharmacist, or a pharmacy customer obtaining the colchicine, said alert indicating that a second active agent (e.g., ketoconazole or ritonavir) is being concomitantly administered to the patient and that prior to the colchicine being dispensed, the colchicine dosing regimen must be reviewed and, if necessary adjusted, so that when the colchicine is delivered to the pharmacy customer obtaining the colchicine it is delivered along with instructions for the colchicine to be taken in accordance with a dosing regimen of no more than one about 0.6 mg colchicine dose to start (e.g., following the onset of the acute gout attack or the first sign of a gout flare) followed by either: no additional colchicine doses within about 12, 24, 48, or 72 hours, or at least one additional colchicine dose within about 12 hours and no more frequently than once every hour and wherein each additional colchicine dose is no greater than about 0.6 mg, and wherein the patient ingests the colchicine as instructed.

The drug-drug interaction alert is preferably issued as one or both of a written warning on a display screen of the pharmacy management computer system, and a printed warning. The printed warning may be attached to or packaged with the dispensed prescription.

In one aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier indicating that the ketoconazole is prescribed so that 200 mg of ketoconazole is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another preferred aspect, the identifier indicating that ketoconazole is being concomitantly administered to the patient is an identifier indicating that the second active agent is ketoconazole and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ketoconazole is prescribed so that about 200 mg of ketoconazole is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

A preferred dosing regimen calls for ingestion of colchicine to be continued until a total of no more than 1.2 mg or 2.4 mg of colchicine has been ingested, after which ingestion of colchicine is to be stopped, e.g., for at least 2, 3, 4, 5, 6, or 7 days, or until a subsequent acute gout flare, or the first sign of a subsequent gout flare, occurs.

In another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier indicating that the ritonavir is prescribed so that 200 or 1200 mg of ritonavir is to be ingested by the patient daily, in which case the dosing regimen for colchicine is preferably one about 0.6 mg colchicine dose to start, optionally followed by additional colchicine doses, e.g., 0, 1, 2, 3, or 4 additional colchicine doses within 24 hours of about 0.3 mg ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11, or 12 hours (e.g., every 2, 3, 4, 5, or 6 hours) after the preceding colchicine dose. In another embodiment, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily, in which case the colchicine dosing regimen is one about 0.6 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours (e.g., every six to eight hours) after the preceding colchicine dose. In one embodiment, the dosing regimen calls for the about 0.3 mg colchicine dose every six to eight hours. In another embodiment, the dosing regimen calls for one dose of the colchicine every eight to twelve hours.

In yet another aspect, the identifier indicating that ritonavir is being concomitantly administered to the patient is an identifier indicating that the second active agent is ritonavir and is linked to at least one further identifier, entered into a second computer readable storage medium in functional communication with a computer, the second storage medium being the same as or different from the first storage medium, and the further identifier indicating that the ritonavir is prescribed so that about 1200 mg of ritonavir is to be ingested by the patient daily and the dosing regimen is one about 0.3 mg colchicine dose to start, followed by an about 0.3 mg colchicine dose ingested every 2, 3, 4, 5, 6, 7, or 8 hours (e.g., every eight to twelve hours) after the preceding colchicine dose.

Also disclosed herein is a dosage adjustment method for administering colchicine to a patient to treat a medical condition, the patient concomitantly treated with a second active agent. The second active agent may be, for example, ritonavir, ketoconazole, cyclosporine, verapamil, or diltiazem. The method comprises determining a first colchicine dosing regimen (the colchicine dosing regimen suitable for administration in the absence of co-administration with a second active agent, which dosing regimen may consist of one or more doses of colchicine); and determining a second active agent dosing regimen; and administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient according to a second colchicine dosing regimen, which may consist of one or more reduced colchicine doses. The second colchicine dosing regimen is a fraction of the first colchicine dosing regimen, where the fraction is obtained by administering reduced colchicine doses or by reducing the frequency of colchicine doses, and wherein the fraction is less than or equal to about ⅔ or less than or equal to about ½ or less than or equal to about ⅓.

According to this embodiment, upon the administering the second active agent to the patient at the second active agent dosing regimen while concomitantly administering colchicine to the patient at the second colchicine dosing regimen, the therapeutic circulating level of colchicine is achieved in the patient. Preferably, the fraction is selected from 1/12, 1/6, ¼, ⅓, 5/12, and ½, more preferably, the fraction is ⅓ or ½. In one embodiment, if the second colchicine dosing regimen comprises a "first" colchicine dose, and one or more "subsequent" colchicine doses, each subsequent colchicine dose may be the

same as the first dose, or a fraction of the first dose. The fraction is selected from about 1/12, about 1/6, about 1/4, about 1/3, about 5/12, about 1/2, and about 7/12, e.g., about 1/2 or about 2/3. In one example, the second colchicine dosing regimen is once-a-day, twice-a-day, three-times-a-day or four-times-a-day. In a variation of this example, the initial treatment day in, a second colchicine dosing regimen that lasts for more than one day, has one more dose administered than are administered each subsequent day.

Preferably the second active agent is selected from ketoconazole, cyclosporine, ritonavir, verapamil, or diltiazem. The specific conditions are selected from gout, FMF, thrombocytopenic purpura, and Behçet's disease. In one embodiment, the gout is an acute gout flare and the colchicine treatment schedule is an acute treatment schedule adapted for treatment of acute gout flares, or the gout is chronic gout, and the colchicine treatment schedule is a chronic treatment schedule adapted for prophylaxis, or prevention, of flares. In another embodiment, the fraction of colchicine administered to the patient concomitantly with a second active agent that is a CYP3A4 or P-gp inhibitor is 1/3 or 1/2 the original intended amount of colchicine and treatment with colchicine is initiated subsequent to or at the same time as initiation of treatment with the second active agent.

Colchicine is one of the most widely used drugs for treating familial Mediterranean fever (FMF). It has been reported that 5-10% of FMF patients do not show a beneficial response to colchicine administration. A polymorphism in the ABCB1 gene, the "ABCB1 3435 C to T polymorphism" has been reported to correlate with this lack of response to colchicine treatment, with patients with the homozygous TT genotype exhibiting the most pronounced "non-responder" phenotypes.

Accordingly, in another aspect, provided herein is a method for treating a patient suffering from FMF, which patient is a colchicine non-responder. Preferably, the patient is homozygous for the TT genotype of the ABCB1 3435 C to T polymorphism. The method entails the concomitant administration of a P-gp inhibitor and colchicine to the patient. Exemplary P-gp inhibitors include ketoconazole and ritonavir. Preferred dosages of the P-gp inhibitor for this purpose correspond to those called for in the prescribing information for the drug in question. For ketoconazole, an exemplary dosage is 200 mg per day. For ritonavir, an exemplary dosage is 200 or 1200 mg per day. Specific colchicine dosing regimens for this purpose are the same as used for treatment of FMF in responders, though the doses of colchicine administered may be increased as tolerated, e.g., up to two to three times the typical doses.

The following examples further illustrate aspects of this disclosure but should not be construed as in any way limiting its scope. In particular, the conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

EXAMPLES

Example 1

Pharmacokinetic Study in Healthy Adults of Single vs. Multiple Oral Doses of Colchicine Tablets

This study was a single-center, open-label, single-sequence, two-period study to evaluate the pharmacokinetic profile of colchicine following single and multiple oral doses of colchicine tablets, 0.6 mg, in healthy volunteers.

In Period 1, study subjects received a 0.6-mg dose of colchicine after an overnight fast of at least 10 hours. In Period 2, subjects received a 0.6 mg dose of colchicine in the morning and the evening (approximately 12 hours later) for 10 days (steady state regimen). Subjects received a light breakfast served 60 minutes following dose administration in the morning and the evening dose was administered 90 minutes after an evening meal on Days 15 through 24 only. On Day 25, the colchicine dose was administered after an overnight fast of at least 10 hours and lunch was served 4 hours post-dose. Study periods were separated by a 14-day washout. Following the single dose and the last dose of the multiple dose regimen (beginning on the mornings of Day 1 and Day 25, respectively), blood samples were collected (6 mL each) from each subject within 1 hour prior to dosing and after dose administration at study hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 (while confined) and 36, 48, 72, and 96 (on an outpatient basis). Plasma concentrations of colchicine and its metabolites were determined using validated LC/MS-MS methods.

Thirteen healthy, non-smoking subjects with a mean age of 25.5 years (range 19 to 38 years) and within 15% of ideal body weight were enrolled in this study. All subjects completed both dosing periods according to protocol.

After a single dose, plasma concentrations are no longer quantifiable 24 hours post-dose in all but 1 subject. After the last dose of the steady state regimen, concentrations remained quantifiable for 48 to 72 hours. Review of individual subject data shows that no subject experienced a secondary colchicine peak, either following a single dose or upon multiple dosing.

All 2-O-demethylcolchicine (2-DMC) concentrations were below the level of quantitation (LOQ, 0.2 ng/mL) and only one sample from 1 subject (of 13 subjects) had a detectable 3-O-demethylcolchicine (3-DMC) concentration, which was near the level of quantitation. Therefore, metabolites are not discussed further.

In healthy adults, colchicine appears to be readily absorbed when given orally, reaching a mean maximum plasma concentration of 2.5 ng/mL in 1.5 hours after a single dose. The drug is distributed widely, with an apparent volume of distribution of 540 L, greatly exceeding total body water. The elimination half-life as calculated following a single oral dose is approximately 5 hours. Levels were not detectable by 24 hours post-dose and this is therefore not an accurate estimate. Pharmacokinetic parameter values are summarized in the table below.

Review of trough plasma concentrations indicates that steady state was attained by approximately the eighth day of dosing for most subjects. Colchicine may have a diurnal variation reflected in the observed Cmin concentrations at steady state. Cmin concentrations prior to the morning dose are approximately 12% higher than the Cmin concentrations prior to the evening dose (Day 23 and Day 24). The mean Cmin concentration observed on Day 25 was 0.907 ng/mL.

Colchicine accumulated following administration of multiple doses to an extent greater than expected. Exposure was nearly two-fold higher (approximately 1.7 based on AUC [Day 25 $AUC_{0-\tau}$/Day 1 $AUC_{0-\infty}$.] and approximately 1.5 based on Cmax [Day 25 C_{max}/Day 1 C_{max}]). This observation could be attributable to an underestimation of AUC∞ following a single dose. With the higher plasma levels that occur with repeated dosing, a longer terminal elimination half-life is apparent, 26.6 hours. Pharmacokinetic parameter values are summarized in Tables 3-5.

TABLE 3

Colchicine Pharmacokinetic Parameter Values Following Administration of A Single Oral Dose of Colchicine 0.6 mg in Healthy Adults (N = 13)

	MEAN	STDEV	% CV	MEDIAN	MIN	MAX
AUC_{0-t} (pg-hr/mL)	10494.66	3544.08	33.77	10560.90	4812.88	18091.85
AUC_{0-inf} (pg-hr/mL)	12268.18	4422.08	36.05	11451.45	7252.66	23801.68
Cmax (pg/mL)	2450.15	702.11	28.66	2480.00	1584.00	3977.00
Tmax (hr)	1.50	0.54	36.00	1.50	1.00	3.00
K_{el} (1/hr)	0.1829	0.0592	32.38	0.1992	0.0359	0.2443
$T_{1/2}$ (hr)	4.95	4.43	89.54	3.48	2.84	19.29

TABLE 4

Colchicine Pharmacokinetic Parameter Values Following Administration of Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults (N = 13)

	MEAN	STDEV	% CV	MEDIAN	MIN	MAX
AUC_{0-t} (pg-hr/mL)	43576.96	9333.26	21.42	41925.10	29328.78	58265.35
$AUC_{0-\tau}$ (pg-hr/mL)	20366.61	3322.12	16.31	20423.08	13719.18	25495.25
AUC_{0-inf} (pg-hr/mL)	54198.77	9214.54	17.00	54113.43	37599.76	67944.65
C_{max} (pg/mL)	3553.15	843.45	23.74	3734.00	1977.00	4957.00
C_{min} (pg/mL)	906.51	152.19	16.79	903.50	636.23	1149.67
C_{ave} (pg/mL)	1697.22	276.84	16.31	1701.92	1143.26	2124.60
T_{max} (hr)	1.31	0.60	45.61	1.00	0.50	3.00
K_{el} (1/hr)	0.0267	0.0044	16.34	0.0261	0.0206	0.0333
$T_{1/2}$ (hr)	26.60	4.33	16.26	26.51	20.82	33.65

TABLE 5

Mean (% CV) Colchicine Pharmacokinetic Parameter Values Following Administration of Single and Multiple (b.i.d.) Oral Doses of Colchicine 0.6 mg in Healthy Adults

	Vd/F (L)	CL/F (L/hr)
Colchicine 0.6-mg Single Dose (N = 13)		
Day 1	341 (54.4)	54.1 (31.0)
Colchicine 0.6 mg b.i.d. × 10 days		
Day 25	1150 (18.73)	30.3 (19.0)

CL = Dose/AUC_{0-t} (Calculated from mean values)
Vd = CL/Ke (Calculated from mean values)

In tables, the parameter CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC0-$_{tau}$; and V_d/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_{\infty} \times K_{el}$). FIG. **1** shows mean colchicine plasma concentrations following administration of single and multiple oral doses of colchicine 0.6 mg in healthy adults.

Example 2

Clinical Drug-Drug Interaction Study of Colchicine and Clarithromycin

A single-center, open-label, one sequence, two-period study was carried out in 23 healthy subjects. On Day 1, a single 0.6-mg dose of colchicine was administered. After completing a 21-day washout period, all subjects received 250 mg of clarithromycin administered twice daily for 7 days (Days 22 through 29), a sufficient dose and duration to inhibit CYP3A4 and Pgp. On the final day (Day 29), a single dose of colchicine was co-administered with the clarithromycin dose. When combined with steady-state clarithromycin, there is a significant increase in exposure to colchicine as compared to when colchicine is given alone: the mean C_{max} and AUC_{0-t} concentrations increased 167% and 250%, respectively. In addition, co-administration of clarithromycin and colchicine resulted in an increase of 233% in the plasma elimination half-life (t½) of colchicine and a 75% decrease in apparent clearance (CL/F). A summary of the mean (% CV) colchicine pharmacokinetic parameters for Day 1 (colchicine administered alone) and Day 29 (colchicine co-administered with steady-state clarithromycin) are given in the table below and illustrated in Table 5.

TABLE 6

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Clarithromycin in Healthy Adults

	Arithmetic Mean (% CV)	
Parameter (units)	Colchicine (N = 23)	Colchicine + Clarithromycin (N = 23)
AUC_{0-t} (ng · hr/mL)	12.37 (37.64)	41.95 (23.31)
AUC_{0-inf} (ng · hr/mL)	15.53 (49.6)	52.62 (22.84)
C_{max} (ng/mL)	2.84 (30.97)	8.44 (17.63)
T_{max} (hr)*	1.50 (0.50-2.00)	1.00 (0.50-2.00)
CL/F (L/hr)	46.8 (43.68)	12.0 (23.75)

FIG. **2** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin in healthy adults. Based on the foregoing data, it is concluded that the dose of colchicine co-administered with clarithromycin should be reduced by ⅔.

Example 3

Clinical Drug-Drug Interaction Study of Colchicine and Cyclosporine

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with cyclosporine on Day 15. Cyclosporine was administered as a single-dose (1×100 mg capsule) on the morning of Day 15. A 14 day washout period was completed after the first colchicine dose on Day 1 and prior to the co-administration of colchicine and cyclosporine doses on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 15. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects were then return to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 16-19 (Period 2). Cyclosporine plasma concentrations were not measured.

TABLE 7

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Cyclosporine in Healthy Adults

	Arithmetic Mean (% CV)	
Parameter (units)	Colchicine (N = 23)	Colchicine + Cyclosporine (N = 23)
AUC_{0-t} (ng · hr/mL)	12.55	39.83
AUC_{0-inf} (ng · hr/mL)	15.00	47.31
C_{max} (ng/mL)	2.72	8.82
T_{max} (hr)*	1.15	1.13
CL/F (L/hr)	48.24	13.42

FIG. **3** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state clarithromycin and steady-state cyclosporine in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with cyclosporine should be reduced by approximately ½ to ¾.

Example 4

Clinical Drug-Drug Interaction Study of Colchicine and Ritonavir

An open-label, non-randomized, single-center, one-sequence, two-period drug interaction study was conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

All subjects received a single 0.6-mg dose of colchicine on Day 1 administered under standard fasting conditions, followed by a 14-day washout period completed on an outpatient basis. At discharge on Day 2, study subjects were instructed to return to the clinical site on the mornings and evenings of Days 15 through 18 to receive two daily dosage amounts of ritonavir (1×100 mg ritonavir capsule twice daily (every 12 hours) on Days 15-18) in a 'directly-observed' fashion; after taking the first dose of ritonavir, subjects remained in the clinic for observation for 1 hour post-dose administration on Day 15. On the evening of Day 18, study participants remained at the clinic for their final study confinement period. In the morning on Day 19, study subjects received a single 0.6 mg colchicine dose with a single 100 mg ritonavir dose and study subjects received the final 100 mg ritonavir dose 12 hours later in the evening on Day 19 under standard fasting conditions.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ritonavir plasma concentrations were not measured.

TABLE 8

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonovir in Healthy Adults: ln-transformed data

	Colchicine Alone	Colchicine + Ritonovir	% Ratio
C_{max} (pg/mL), geometric mean	1798.37	4835.39	268.88
AUC_{0-t} (pg · h/mL), geometric mean	7642.71	27793.08	363.65
AUC_{∞} (pg · h/mL), geometric mean	9551.74	33771.36	353.56

TABLE 9

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ritonavir in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Ritonavir (N = 18)	Colchicine Alone (N = 18)
AUC_{0-t} (ng · hr/mL)	29.05 (30.76)	8.41 (47.46)
$AUC_{0-\infty}$ (ng · hr/mL)	35.28 (29.79)	10.41 (45.48)
C_{max} (ng/mL)	4.99 (25.18)	1.87 (28.19)
T_{max} (hr)	1.5 (1-1.5)	1 (0.5-1.5)
CL/F (L/hr)	18.59 (31.58)	67.93 (39.47)

Following exposure to 100 mg b.i.d.×5 days, there was a significant increase in exposure to a single 0.6-mg colchicine

(approximately 245%). Mean peak colchicine concentration increased by approximately 170%. Total apparent oral clearance was decreased by 70% with co-administration. T_{max} is not affected. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. **4** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ritonavir should be reduced by approximately ½.

Example 5

Clinical Drug-Drug Interaction Study of Colchicine and Ketoconazole

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there will be a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with ketoconazole on Day 19 (AM dose). Ketoconazole was administered for 5 consecutive days [200 mg twice daily (every 12 hours)] beginning on the morning of Day 15, with the last 200 mg ketoconazole dose administered on the evening on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects will be confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects then returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Ketoconazole plasma concentrations were not measured.

TABLE 10

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults: ln-transformed data

	Colchicine Alone	Colchicine + Ketoconazole	% Ratio
C_{max} (pg/mL), geometric mean	2598.28	5078.50	195.46
AUC_{0-t} (pg · h/mL), geometric mean	11087.99	33223.80	299.64
AUC_{∞} (pg · h/mL), geometric mean	13185.92	42143.00	319.61

TABLE 11

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Ketoconazole in Healthy Adults

	Arithmetic Mean (% CV)	
Parameter (units)	Colchicine (N = 23)	Colchicine + Ketoconazole (N = 23)
AUC_{0-t} (pg · hr/mL)	11988.61	34382.82
AUC_{0-inf} (pg · hr/mL)	14314.09	43688.90
C_{max} (pg/mL)	2779.08	5266.92
T_{max} (hr)*	1.00	1.02
CL/F (L/hr)	49301.09	14797.94

*Median (Range) for T_{max}

Following administration of ketoconazole 200 mg b.i.d.×5 days, there was a significant increase in exposure to a single oral dose of colchicine 0.6 mg (C_{max} and AUC_{0-t} increased by 90% and 190%, respectively, and $AUC_{0-\infty}$ increased by about 205%). Total apparent oral clearance decreased by 70% with co-administration. Elimination half-life could not be estimated accurately as plasma concentrations were not quantifiable after 24 hours.

FIG. **4** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state ritonavir and steady-state ketoconazole in healthy adults. Based on the foregoing data, the dose of colchicine co-administered with ketoconazole should be reduced by approximately ½.

Example 6

Clinical Drug-Drug Interaction Study of Colchicine and Azithromycin

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers; there was a 14-day washout between the two periods. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with the azithromycin on Day 19. Azithromycin was administered for 5 consecutive days (2×250 mg once daily [Day 15 only] and then 1×250 mg once daily Days 16-19) beginning on the morning of Day 15, with the last 250 mg azithromycin dose administered on the morning on Day 19. Total study participation, exclusive of up to 28 days of screening, was approximately 24 days, during which subjects were confined on two occasions for a total confinement of approximately 3 days.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Azithromycin plasma concentrations were not measured.

TABLE 12

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults

	Colchicine Alone	Colchicine + Azithromycin	% Ratio
C_{max} (pg/mL), geometric mean	2535.94	2856.22	112.63
AUC_{0-t} (pg · h/mL), geometric mean	10971.51	16090.52	146.66
AUC_{∞} (pg · h/mL), geometric mean	12931.80	18312.83	141.61

TABLE 13

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Azithromycin in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Azithromycin (N = 21)	Colchicine Alone (N = 21)
AUC_{0-t} (ng · hr/mL)	17.16 (37.78)	11.98 (45.81)
$AUC_{0-\infty}$ (ng · hr/mL)	19.61 (39.15)	14.13 (46.73)
C_{max} (ng/mL)	3.05 (39.54)	2.74 (41.52)
T_{max} (hr)	1.5 (0.5-3)	1.0 (0.5-3)
$t_{1/2}$ (hr)	6.71 (68.34)[1]	6.07 (66.15)[1]
CL/F (L/hr)	35.01 (37.26)	50.24 (40.31)

Following administration of azithromycin 500 mg on Day 1 followed by 250 mg×4 days, exposure to colchicine is increased (approximately 46% for AUC_{0-t} and approximately 40% for $AUC_{0-\infty}$). Mean peak colchicine concentration increased by approximately 12% and total apparent oral clearance decreased approximately 30% with co-administration. T_{max} was not affected.

FIG. **5** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 7

Clinical Drug-Drug Interaction Study of Colchicine and Diltiazem

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

As single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with diltiazem ER on Day 21. Diltiazem ER was administered for 7 consecutive days (1×240 mg capsule once daily on Days 15-21) beginning on the morning of Day 15, with the last 240 mg diltiazem ER dose administered on the morning on Day 21. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first diltiazem ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 21. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on an inpatient basis. Subjects returned to the clinic on an outpatient basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration. Diltiazem plasma concentrations were not measured.

TABLE 14

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults

	Colchicine Alone	Colchicine + Diltiazem	% Ratio
C_{max} (pg/mL), geometric mean	2006.42	2583.22	128.75
AUC_{0-t} (pg · h/mL), geometric mean	9154.55	15740.37	171.94
AUC_{∞} (pg · h/mL), geometric mean	11022.30	19902.98	180.57

TABLE 15

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Diltiazem in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Diltiazem (N = 20)	Colchicine Alone (N = 20)
AUC_{0-t} (ng · hr/mL)	17.73	10.04
$AUC_{0-\infty}$ (ng · hr/mL)	22.49	12.03
C_{max} (ng/mL)	2.80	2.17
T_{max} (hr)	1.48	1.15
$t_{1/2}$ (hr)	12.50	5.51
CL/F (L/hr)	463.49	395.83

FIG. **5** shows a pharmacokinetic profile comparison of single-dose colchicine (0.6 mg, alone) and single-dose colchicine (0.6 mg) co-administered with steady-state azithromycin and steady-state diltiazem in healthy adults.

Example 8

Clinical Drug-Drug Interaction Study of Colchicine and Verapamil

This study was an open-label, non-randomized, single-center, one-sequence, two-period drug interaction study conducted in healthy male and female volunteers. Twenty-four (24) non-smoking, non-obese adult volunteers were enrolled. All subjects were dosed and studied as a single cohort, with each subject receiving the same treatment in a non-randomized fashion.

A single dose of colchicine, 0.6 mg, was administered alone on Day 1, and then co-administered with verapamil HCl ER on Day 19. Verapamil HCl ER was administered for 5 consecutive days (1×240 mg tablet once daily on Days 15-19) beginning on the morning of Day 15, with the last 240 mg verapamil HCl ER dose administered on the morning on Day 19. A 14-day washout period was completed after the first colchicine dose on Day 1 and prior to the administration of the first verapamil HCL ER dose on Day 15.

Serial blood samples were collected by individual venipuncture up to 96 hours following drug administration on Day 1 and Day 19. Blood samples for determination of colchicine plasma concentrations were obtained at time zero (pre-dose) and after dose administration at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on a confined basis. Subjects returned to the clinic on a non-confined basis for continued blood sampling collection at 36, 48, 72, and 96 hours post-dose administration on Days 2-5 (Period 1) and Days 20-23 (Period 2). Verapamil plasma concentrations were not measured.

TABLE 16

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults

	Colchicine Alone	Colchicine + Verapamil	% Ratio
C_{max} (pg/mL), geometric mean	2768.77	3639.68	131.45
AUC_{0-t} (pg · h/mL), geometric mean	12256.40	23889.21	194.94
AUC_{∞} (pg · h/mL), geometric mean	14415.79	29556.75	205.03

TABLE 17

Comparison of Single-Dose Colchicine (0.6 mg, Alone) and Single-Dose Colchicine (0.6 mg) Co-Administered with Steady-State Verapamil in Healthy Adults

	Arithmetic Mean (% CV) Median (Range) for T_{max}	
Parameter (units)	Colchicine + Verapamil (N = 24)	Colchicine Alone (N = 24)
AUC_{0-t} (ng · hr/mL)	24.64	13.09
$AUC_{0-\infty}$ (ng · hr/mL)	30.59	15.37
C_{max} (ng/mL)	3.85	2.97
T_{max} (hr)	1.15	1.22
$t_{1/2}$ (hr)	17.17	6.24
CL/F (L/hr)	21.01	43.93

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

All methods described herein can be performed in a suitable order unless otherwise indicated or clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") herein is intended to better illuminate the disclosure and is non-limiting unless otherwise specified. No language in the specification should be construed as indicating that any non-claimed element as essential to the practice of the claimed embodiments. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. The terms wt %, weight percent, percent by weight, etc. are equivalent and interchangeable.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to").

"Concomitant" and "concomitantly" as used herein refer to the administration of at least two drugs to a patient either simultaneously or within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., clarithromycin and the second drug is colchicine, the concomitant administration of the second drug can occur as much as one to two weeks, preferably within one to seven days, after the administration of the first drug. This is because clarithromycin can exert a long-lasting inhibition of CYP3A isozymes so that CYP3A activity in the patient may not return to pre-clarithromycin-administration levels for as much as two weeks after the cessation of clarithromycin administration. If colchicine is the first drug, administration of a second drug would be concomitant if done within 1 to 2 days, preferably 12 to 24 hours.

A "dose" means the measured quantity of a drug to be taken at one time by a patient.

A "dosage amount" means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e. daily). A "daily dosage amount" is the total dosage amount taken in one day, that is, a 24 hour period.

"Dosing regimen" means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or different.

A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In preferred embodiments the patient is human.

"Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

"Risk" means the probability or chance of adverse reaction, injury, or other undesirable outcome arising from a medical treatment. An "acceptable risk" means a measure of the risk of harm, injury, or disease arising from a medical treatment that will be tolerated by an individual or group. Whether a risk is "acceptable" will depend upon the advantages that the individual or group perceives to be obtainable in return for taking the risk, whether they accept whatever scientific and other advice is offered about the magnitude of the risk, and numerous other factors, both political and social. An "acceptable risk" of an adverse reaction means that an individual or a group in society is willing to take or be subjected to the risk that the adverse reaction might occur since the adverse reaction is one whose probability of occurrence is small, or whose consequences are so slight, or the benefits (perceived or real) of the active agent are so great. An "unacceptable risk" of an adverse reaction means that an individual or a group in society is unwilling to take or be subjected to the risk that the adverse reaction might occur upon weighing the probability of occurrence of the adverse reaction, the consequences of the adverse reaction, and the benefits (perceived or real) of the active agent. "At risk" means in a state or condition marked by a high level of risk or susceptibility.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma con-

centration (C), as well as C_{max}, C_n, C_{24}, T_{max}, and AUC. "C_{max}" is the measured plasma concentration of the active agent at the point of maximum, or peak, concentration. "C_{min}" is the measured plasma concentration of the active agent at the point of minimum concentration. "C_n" is the measured plasma concentration of the active agent at about n hours after administration. "C_{24}" is the measured plasma concentration of the active agent at about 24 hours after administration. The term "T_{max}" refers to the time from drug administration until C_{max} is reached. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-\infty}$, AUC_{∞} or AUC_{0-inf} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-\tau}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time τ (tau), where tau is the length of the dosing interval. Other pharmacokinetic parameters are the parameter K_e or K_{el}, the terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; $t_{1/2}$ the terminal elimination half-life, calculated as $0.693/K_{el}$. CL/F denotes the apparent total body clearance after administration, calculated as Total Dose/Total AUC_{∞}; and V_{area}/F denotes the apparent total volume of distribution after administration, calculated as Total Dose/(Total $AUC_{\infty} \times K_{el}$).

"Side effect" means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

The most frequently reported adverse side effects to colchicine therapy are gastrointestinal, specifically abdominal pain with cramps, diarrhea, nausea, and vomiting. Less frequently or rarely reported adverse side effects associated with colchicine therapy include anorexia, agranulocytosis, allergic dermatitis, allergic reactions, alopecia, angioedema, aplastic anemia, bone marrow depression, myopathy, neuropathy, skin rash, thrombocytopenic disorder, and urticaria.

Whether a patient experiences an adverse side effect can be determined by obtaining information from the patient regarding onset of certain symptoms which may be indicative of the adverse side effect, results of diagnostic tests indicative of the adverse side effect, and the like.

Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the subject matter recited in the claims appended hereto are included to the extent permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A method of treating a patient in need of treatment for prophylaxis of gout flares with colchicine, comprising

orally administering an adjusted daily dosage amount of colchicine to the patient who is receiving concomitant administration of verapamil,

wherein the adjusted daily dosage amount of colchicine is 50% to 75% of an intended daily dosage amount of colchicine,

wherein the intended daily dosage amount of colchicine is a dosage amount suitable for the patient if the patient were not receiving concomitant verapamil, wherein the intended daily dosage amount of colchicine suitable for the patient if the patient were not receiving concomitant verapamil is 0.6 mg twice daily or 0.6 mg once daily, and wherein the concomitantly administered dose of verapamil is 240 mg per day.

2. The method of claim **1**, wherein the adjusted daily dosage amount is 50% of the intended daily dosage amount.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,440,722 B2
APPLICATION NO. : 13/454255
DATED : May 14, 2013
INVENTOR(S) : Matthew W. Davis

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

In column 1, line 9, after "Continuation" insert -- of --.

In column 1, line 14, delete "Dec. 17, 2008" and insert -- January 14, 2009 --, therefor.

In column 3, line 53, delete "that that" and insert -- that --, therefor.

In column 4, line 48, delete "●" and insert -- ○ --, therefor.

In column 4, line 55, delete "▲" and insert -- Δ --, therefor.

In column 4, line 55, delete "●" and insert -- ○ --, therefor.

In column 4, line 56, delete "■" and insert -- □ --, therefor.

In column 4, line 62, delete "▲" and insert -- Δ --, therefor.

In column 4, line 62, delete "●" and insert -- ○ --, therefor.

In column 4, line 63, delete "■" and insert -- □ --, therefor.

In column 5, line 2, delete "▲" and insert -- Δ --, therefor.

In column 5, line 2, delete "●" and insert -- ○ --, therefor.

In column 5, line 3, delete "■" and insert -- □ --, therefor.

In column 6, line 56, delete "in a" and insert -- in --, therefor.

In column 8, line 67, delete "reduce" and insert -- be reduced --, therefor.

In column 9, line 2, delete "wherein the" and insert -- the --, therefor.

Signed and Sealed this
Thirteenth Day of August, 2013

Teresa Stanek Rea

Teresa Stanek Rea
Acting Director of the United States Patent and Trademark Office

In column 9, line 13, after "amount" insert -- is --.

In column 9, line 43, delete "reduce" and insert -- be reduced --, therefor.

In column 9, line 46, delete "wherein the" and insert -- the --, therefor.

In column 9, line 57, after "amount" insert -- is --.

In column 10, line 20, delete "reduce" and insert -- be reduced --, therefor.

In column 10, line 23, delete "wherein the" and insert -- the --, therefor.

In column 10, line 35, after "amount" insert -- is --.

In column 11, line 11, delete "reduce" and insert -- be reduced --, therefor.

In column 11, line 22, after "amount" insert -- is --.

In column 12, line 33, delete "amount of" and insert -- amount for --, therefor.

In column 12, line 41, before "Colchicine" insert -- Table 2 --.

In column 13, line 11, delete "levels[1]" and insert -- levels --, therefor.

In column 13, line 27, delete "levels[1]" and insert -- levels --, therefor.

In column 15, line 17, delete "9" and insert -- 9, --, therefor.

In column 16, line 2, delete "9" and insert -- 9, --, therefor.

In column 16, line 58, delete "the administering" and insert -- administering --, therefor.

In column 18, line 24, delete "are" and insert -- were --, therefor.

In column 18, line 53, delete "Cmin" and insert -- C_{min} --, therefor.

In column 18, line 54, delete "Cmin" and insert -- C_{min} --, therefor.

In column 18, line 55, delete "Cmin" and insert -- C_{min} --, therefor.

In column 18, line 57, delete "Cmin" and insert -- C_{min} --, therefor.

In column 18, line 62, delete "Cmax" and insert -- C_{max} --, therefor.

In column 18, line 63, delete "AUC∞" and insert -- AUC_{∞} --, therefor.

In column 19, line 10, delete "Cmax" and insert -- C_{max} --, therefor.

In column 19, line 12, delete "Tmax" and insert -- T_{max} --, therefor.

In column 19, line 41, delete "Vd/F" and insert -- V_d/F --, therefor.

In column 19, line 48, delete "Vd = CL/Ke" and insert -- $V_d = CL/K_e$ --, therefor.

In column 19, line 52, delete "AUC0-$_{tau}$;" and insert -- $AUC_{0\text{-}tau}$; --, therefor.

In column 20, line 37, delete "Pgp" and insert -- P-gp --, therefor.

In column 20, line 45, delete "(t1/2)" and insert -- ($t_{1/2}$) --, therefor.

In column 20, lines 49-50, after "below" delete "and illustrated in Table 5".

In column 20, line 64, after "T_{max} (hr)" delete "*".

In column 21, lines 31-32, delete "were then return" and insert -- then returned --, therefor.

In column 21, line 43, after "Arithmetic Mean" delete "(% CV)".

In column 21, line 50, after "T_{max} (hr)" delete "*".

In column 22, line 1, delete "will be" and insert -- was --, therefor.

In column 22, line 38, delete "Ritonovir" and insert -- Ritonavir --, therefor.

In column 22, line 41, delete "Ritonovir" and insert -- Ritonavir --, therefor.

In column 23, line 24, delete "will be" and insert -- was --, therefor.

In column 23, lines 36-37, delete "will be" and insert -- were --, therefor.

In column 24, line 6, after "Arithmetic Mean" delete "(% CV)".

In column 24, line 16, after "*Median" delete "(Range)".

In column 25, line 29, delete "(68.34)[1]" and insert -- (68.34) --, therefor.

In column 25, line 29, delete "(66.15)[1]" and insert -- (66.15) --, therefor.

In column 25, line 57, delete "As" and insert -- A --, therefor.

In column 26, line 30, after "Arithmetic Mean" delete "(% CV)".

In column 26, line 31, after "Median" delete "(Range)".

In column 27, line 32, after "Arithmetic Mean" delete "(% CV)".

In column 27, line 33, after "Median" delete "(Range)".

EXHIBIT R

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICALS U.S.A., INC., Plaintiff, vs. PAR PHARMACEUTICAL, INC., and PAR PHARMACEUTICAL COMPANIES, INC., Defendants.	C.A. No. 13-cv-1524-SLR

DECLARATION OF CHAD S. BOOMERSHINE, M.D., Ph.D.

I, Chad S. Boomershine, M.D., Ph.D., declare as follows:

1. I am a Board Certified physician in internal medicine and rheumatology. I received my M.D. and Ph.D. from the Ohio State University College of Medicine and Public Health in 2002. Following medical school, I completed a residency in internal medicine in 2004 and clinical fellowship in rheumatology in 2005 both at Vanderbilt University.

2. I currently am Medical Director of Boomershine Wellness Centers in Nashville, Tennessee. I also am an Assistant Clinical Professor of Medicine at Vanderbilt University.

3. As a Board Certified Rheumatologist, I specialize in the care of patients with rheumatic diseases including gout, arthritis, fibromyalgia, chronic fatigue syndrome as well as the rare disease Familial Mediterranean Fever ("FMF").

4. I understand that recent estimates from the Center for Disease Control and American College of Rheumatology indicate that more than 8.3 million people in the United States suffer from gout. Gout is the most common form of inflammatory arthritis. In contrast, by comparison the number of patients in the United States suffering from FMF is very small. FMF is classified as a rare disease because it affects less than 200,000 people in the United States.

5. Over my twelve year career, I have treated hundreds of patients suffering from gout. In comparison, in that same time period, I have only treated a single patient suffering from FMF. In my experience, my limited exposure to FMF patients is not uncommon for a rheumatologist given the lack of prevalence of the disease in the United States.

6. I routinely prescribe Colcrys®, an orally administered pharmaceutical product containing the active ingredient colchicine, for patients to treat and prevent gout flares. Over the past three years, I have frequently prescribed Colcrys® for the treatment and prevention of gout flares. In comparison, in that same time period, I have not once prescribed Colcrys® to treat FMF.

7. I understand that in 2009 the United States Food and Drug Administration ("FDA") approved Colcrys® for the treatment and prevention of gout flares. I am also aware that Colcrys® remains the only FDA approved oral colchicine product available for physicians to prescribe for the prevention and treatment of gout flares.

8. As a practicing physician, I am aware that the FDA does not regulate or mandate the choice of medications prescribed by a physician. Rather, a physician's prescribing decision is generally based on knowledge, experience, training, review of the medical literature and review of the Physician's Desk Reference or package insert for the brand drug, which is the first version of the drug that comes to market. By the time a generic version of a branded drug becomes available, I and other physicians typically have had years of experience prescribing the brand drug.

9. My knowledge of approved indications also comes from the indications included in the brand name drug label. I have never relied on any information from a generic drug company when making prescribing decisions. I have never reviewed a label from a generic drug maker when deciding whether to prescribe a drug, the dose or dosing frequency of a drug, or the indication for which to prescribe a drug. Moreover, I have never received and to the best of my recollection have never seen a generic drug label, including its approved indications. Based on

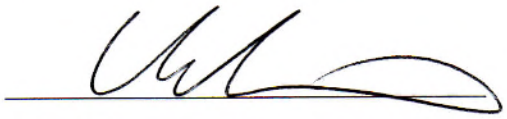
my interactions with other physicians I believe my experience as described in this paragraph to be similar to that of most physicians.

10. Prior to 2009, unapproved colchicine was prescribed in the United States for the treatment and prevention of gout flares, and the only way to prescribe the drug before that time was to use the term "colchicine." In 2009, Colcrys® was approved by the FDA. Based on my experience reviewing patient histories as well as through interactions with other physicians that use colchicine to treat gout, many physicians have maintained the practice of using the phrase "colchicine" (instead of Colcrys®) when writing prescriptions for patients suffering from gout flares.

11. In my experience practicing over the past twelve years and in discussing the use of generic products with my colleagues, attending seminars and reading literature, most prescribing physicians assume that when a generic drug is made available it can be prescribed for any approved indication associated with the brand name drug. Colcrys® is approved for the prevention and treatment of gout flares as well as treatment of FMF. Accordingly, if a generic version of Colcrys® is made available for treatment of FMF, I would expect that practicing physicians would also start prescribing "colchicine" for gout patients.

12. Physicians make the decision to prescribe a particular drug. They generally are not involved in the decision of how to fill the prescription. In particular, physicians do not generally control whether a pharmacist fills a prescription for a given drug with a brand drug product or with a generic product. Unless physicians specify on the prescription that only the brand drug should be dispensed ("Dispense as Written" or "DAW" or "Brand Only") pharmacists will generally fill that prescription with a generic version due to cost concerns. Further, I am aware that many states have substitution laws that require a pharmacist to distribute generic versions of drugs (if available) instead of the brand named drug, unless specifically prohibited by the prescribing physician. One effect of these prescribing practices is that pharmacists will tend to fill a prescription for colchicine with a generic version of Colcrys®, if one is available.

I declare that the foregoing statements are true and accurate, and that this declaration is made under penalty of perjury under the laws of the State of Tennessee and the United States.



Chad S. Boomershine, M.D., Ph.D.

Dated April 30, 2014

EXHIBIT S

NATIONAL ASSOCIATION OF
BOARDS OF PHARMACY

2014

ORGANIZATIONAL LAW

LICENSING LAW

DRUG LAW

CENSUS DATA

Survey *of* Pharmacy Law

Including all 50 states, DC, Guam, and Puerto Rico

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Carmen A. Catizone, MS, RPh, DPh
Executive Director/Secretary

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19. Drug Product Selection Laws

State	State Drug Formulary	Two-line Rx Format	Permissive or Mandatory*	How to Prevent Substitution	Cost Savings Pass-on	Patient Consent**
Alabama	None	Yes	P, BBB	A	U	No
Alaska	None	No	P	B	T	Yes
Arizona	None	No	P	J	U	Yes
Arkansas	None	No	P	B	T	Yes
California	None	No	P	EE	T	Yes
Colorado	None	No	P	J	S	Yes GGG
Connecticut	None	No	P	E, F	S	Yes
Delaware	None	No	P	E	S	Yes
District of Columbia	Positive	No	P	B	T	Yes
Florida	Negative L	No	M	B	S	Yes
Georgia	None	No	P	C	N	Yes
Guam	None	No	P	G	T	No DD
Hawaii	Positive AA, K	No	P	CC, PP	T	Yes
Idaho	None	No	P	WW	U	Yes
Illinois	Positive KK	No	P	AAA	T	No YY
Indiana	None	Yes	P	A	O	Yes II
Iowa	None	No	P	I	X	Yes
Kansas	None	Yes	M	A, I	T	Yes II
Kentucky	Negative	Yes (conditional)	M	B, H, Y	T	Yes
Louisiana	None K	No	P	R	HH	Yes
Maine	None	No	P	B, R	V	Yes
Maryland	None K	No	P	H, I	HH	Yes
Massachusetts	Positive K	No	M	B	T	No
Michigan	None	No	P	E	S	No
Minnesota	Negative	No	M	E	S	Yes
Mississippi	None	Yes	M	A	T	Yes
Missouri	None	Yes	P	A	T	Yes
Montana	None	No	P	CCC	S, T	Yes
Nebraska	Positive K	No	P	B	U	Yes
Nevada	Positive K	No	M	B	T	No
New Hampshire	Positive K	No	P	B	T	Yes
New Jersey	Positive	Yes	M	A	T	No
New Mexico	None	No	P	G	S	No
New York	Positive	No Z	M	D, H	T	Yes
North Carolina	None	Yes (optional)	P	A, B	T	Yes UU
North Dakota	None	No Z	P	B	T	Yes
Ohio	None	No	P	E	T	Yes
Oklahoma	None	No	W	W	U	W
Oregon	None	No	P	ZZ	T	No
Pennsylvania	None K	No	M	C	T	Yes
Puerto Rico	None	No	M	LL	T	Yes
Rhode Island	None JJ	No	M, DD	C, GG	S	No
South Carolina	None	Yes	P	A	U	Yes
South Dakota	None K	No	P	B	U	Yes
Tennessee	None	No	P	TT	S	No
Texas	None K	No	P	CC	T	Yes
Utah	Positive K	Optional	P	B, Q	U	Yes
Vermont	None K	No	P	FF	V	No
Virginia	None K	No	P	H	T	Yes
Washington	None	Yes	M	A	BB	No DD
West Virginia	K	No Z	B, M, O, HH	B, F, CC	S	Yes
Wisconsin	Positive K	No	P	B	HH	Yes
Wyoming	None K	No	P	I	T	No

* State laws either permit the pharmacist to substitute or mandatorily require the pharmacist to substitute a generic version of the prescribed drug if all prescription requirements are met.

** Yes – Includes states where consent is required and those that require the patient to be notified/informed of substitution.

Colored text denotes change from 2013 edition. — Indicates information is not available.

19. Drug Product Selection Laws (cont.)

State	Has State Designated a List of Drugs That Are Not Substitutable (ie, Narrow Therapeutic Index Drugs)?	Does State Have Any Interchangeability Requirements for Biosimilars/Biologics?
Alabama	No	No
Alaska	No	No
Arizona	No K	No
Arkansas	No K	No EEE
California	No	No
Colorado	No	No
Connecticut	No	No
Delaware	K	N/A
District of Columbia	No	No
Florida	Yes	No HHH
Georgia	No	—
Guam	—	—
Hawaii	Yes PP	Yes FFF
Idaho	Yes	No
Illinois	No	No HHH
Indiana	No	No
Iowa	No	No
Kansas	K	No
Kentucky	Yes QQ	No
Louisiana	No K	No
Maine	Yes	No
Maryland	No	No
Massachusetts	No MM	Yes K, MM
Michigan	No	—
Minnesota	Yes NN	No
Mississippi	No	No
Missouri	No	No
Montana	No	No
Nebraska	No	Yes III
Nevada	No	No
New Hampshire	No	No
New Jersey	No	No
New Mexico	No	No
New York	No	No
North Carolina	Yes VV	No
North Dakota	No	No
Ohio	No	No
Oklahoma	No	No
Oregon	No	Yes
Pennsylvania	Yes	Yes
Puerto Rico	K	—
Rhode Island	Yes RR	—
South Carolina	No	No
South Dakota	No	No DDD
Tennessee	No XX	No
Texas	No OO	No
Utah	No	No
Vermont	No	No
Virginia	No	Yes JJJ
Washington	No	No
West Virginia	No	No K
Wisconsin	No	Yes SS
Wyoming	No	No

Colored text denotes change from 2013 edition.
— Indicates information is not available.

19. Drug Product Selection Laws (cont.)

LEGEND

A — Prescriber's signature on appropriate line of two-line prescription.

B — To prevent DPS prescriber must expressly indicate in some manner. (AK, AR, SD – Prescriber must write in own handwriting in addition to signature "Brand Necessary." MA – Must indicate "No Substitution." ND – Prescriber must write in own handwriting in addition to signature "Brand Medically Necessary." NH – The prescribing practitioner handwrites "medically necessary" on each paper prescription, or uses electronic indications when transmitted electronically, or gives instructions when transmitted orally that the brand name drug product is medically necessary. NV – Prescriber must write in own handwriting "Dispense as Written.")

C — Prescriber's signature shall validate the prescription and, unless the prescriber handwrites (RI – Indicates) "Brand Necessary" or "Brand Medically Necessary," shall designate approval of drug substitution by the pharmacist.

D — Prescriber must indicate "Dispense as Written" in the designated box, or positively indicate brand for electronic prescriptions.

E — Prescriber must write in own handwriting: "DAW" or "Dispense as Written." (DE – "Brand necessary" or "brand medically necessary." MN – Unless the prescription is transmitted electronically in accordance with the Code of Federal Regulations, Title 42, Section 423.)

F — Prescriber indicates "Medically Necessary" in own handwriting.

G — A licensed practitioner shall prohibit drug product selection by handwriting the words "No Substitution" or the diminutive "No Sub" on the face of the prescription.

H — "Brand Medically Necessary" to be handwritten on the face of the prescription by the prescriber for Medicaid patients, or product selection is allowed. (NY – An alternative provision that requires positive indication for electronic prescriptions. VA – For all non-Medicaid patients, phrase must be included, but not required to be handwritten.)

I — Prescriber must expressly indicate that substitution is not allowed.

J — Prescriber must handwrite "Dispense as Written" or hand initial a preprinted box labeled "Dispense as Written." May also be done electronically.

K — Uses FDA Therapeutic Equivalency List ("Orange Book"). (HI – Plus deletions and additions by the Drug Product Selection Board administered by the Department of Health, Food and Drug Branch. KS – Uses Orange Book – National Formulary as official compendium. KSA 65-656. MA – Plus "additional list" and "exception list." PA – Plus narrow therapeutic index.)

L — Each pharmacy is to develop DPS List.

M — Mandatory.

N — The pharmacist shall dispense the lowest retail priced drug product that is in stock, and which, in the pharmacist's opinion, is pharmaceutically and therapeutically equivalent to the prescribed drug.

O — Unless in the pharmacist's professional judgement.

P — Permissive. (AL – If authorized by prescriber.)

Q — Allows use of preprinted "Do Not Substitute" checkbox.

R — Box must be checked to prevent DPS.

S — Full savings must be passed on to consumer.

T — Drug dispensed must be less or no more expensive than drug prescribed. (IL – Refer to 225 ILCS 85/25.)

U — No cost savings pass-on requirement mentioned.

V — No more than usual and customary charge for prescribed drug.

W — O.S. (1961) states that it is unlawful for a pharmacist to substitute without the authority of the prescriber or purchaser.

X — Must pass on 50% of difference between brand name cost and generic cost.

Y — May indicate in manner of his or her choice on the prescription "Do Not Substitute," except that the indication shall not be preprinted on a prescription.

Z — One-line format.

AA — Product selection laws under jurisdiction of Department of Health, Food and Drug Branch.

BB — Must pass on 60% of difference between brand name cost and generic cost. Drug dispensed must be less expensive than drug prescribed.

Legend continued on page 70

NABP*LAW* Online Search Terms

Drug Product Selection Laws *(type as indicated below)*

- biosimilar
- "drug product selection"
- formulary selection
- product substitution requirements
  "narrow therapeutic index"
- substitution authorize requirements
- substitution generic requirements

19. Drug Product Selection Laws (cont.)

LEGEND — cont.

CC — Prescriber must indicate "brand necessary" or "brand medically necessary" in own handwriting or product selection is allowed.

DD — Patient may request that brand name be dispensed, but prescriber must authorize generic.

EE — Prescriber may indicate orally or in own handwriting "Do Not Substitute" or similar words. Allows use of a preprinted "Do Not Substitute" box, provided that the prescriber personally initials the box.

FF — Prescriber must write "brand necessary," "no substitution," "dispense as written," or "DAW" in own handwriting. (See Sec. 4. 18 V.S.A. §4606 Brand Certification.)

GG — Patient may request, in writing, that the brand name be dispensed.

HH — Drug dispensed must be less expensive than drug prescribed.

II — Patient must be informed/notified (KS – Regulation KAR 68-2-20).

JJ — Director of Health designates items on Drug Product Selection List.

KK — Positive Formulary and "Orange Book."

LL — Prescriber must write on the face of the prescription in own handwriting the phrase, "Do not interchange."

MM — Formulary commission, a separate Department of Public Health agency, makes those decisions.

NN — But they are still substitutable, it is just not mandatory. There are currently no drugs on the list.

OO — The Board has the authority to publish a list of narrow therapeutic index drugs that cannot be substituted. However, the current list contains no drugs.

PP — Refer to the Department of Health, Food and Drug Branch.

QQ — Refer to KAR 2:116, drug products with therapeutic problems.

RR — State utilizes a negative drug formulary.

SS — WI Statute 450.13(1) specifies that it must be therapentically equivalent as designated by the FDA "Orange Book" ratings.

TT — The prescriber shall, in the prescriber's own handwriting, include on the prescription the following language (but not limited to): (1) "Brand name medically necessary," "dispense as written," "medically necessary," "brand name," "no generic"; or (2) Any abbreviation of the language in the section above; or (3) Any other prescriber handwritten notation, such as circling a preprinted "dispense as written" on the prescription order, that clearly conveys the intent that a brand name is necessary for the patient.

UU — For narrow therapeutic index drugs only.

VV — May substitute with documented consent of treating prescriber and patient.

WW — If a prescriber orders by any means that a brand name drug must be dispensed, then no drug selection is permitted.

XX — Can dispense generic epilepsy drugs on the original prescription as long as that brand is maintained. Before the pharmacist can change the brand of the generic, permission must be obtained from the prescriber and the patient.

YY — Except for anti-epileptic drugs (225 ILCS 85/26(c)).

ZZ — A practitioner may specify in writing, by a telephonic communication or by electronic transmission that there shall be no substitution for the specified brand name drug in any prescription. May not use default values on the prescription. For an electronically transmitted prescription, the prescriber or prescriber's agent shall clearly indicate substitution instructions in the prescription drug order as well as all relevant electronic indicators sent as part of the electronic prescription transmission.

AAA — Prescriber must indicate "may not substitute" by marking a designated box. See Section 225 ILCS 85/25.

BBB — Two lines on prescriptions are mandatory. A pharmacist can only substitute if indicated by physician signing that line; however, if a prescription from a practitioner who is located in another state and does not expressly prohibit substitution, a pharmacist is permitted to substitute. Public school employees are exempt from this provision.

CCC — "Brand name medically necessary" shall be handwritten (or printed if electronically generated) on the face of the prescription if it is medically necessary that an equivalent drug product not be selected.

DDD — Product must be A or AB rated as defined by the "Orange Book."

EEE — The Arkansas Board recognizes the FDA Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") as the basis for the determination of generic equivalency within the limitations stipulated in that publication. The Arkansas General Assembly enacted legislation to allow therapeutic substitution effective August 15, 2013. The rules and regulations process is pending.

FFF — If permitted by the "Orange Book."

GGG — Patient must be notified orally and in writing.

HHH — Interchangeability for biosimilars/ biologics only if approved by FDA.

III — Must obtain prescriber approval to substitute a drug product that is not equivalent.

JJJ — Definition of "biosimilar," "interchangeable," and "reference biological product" in §54.1-3401; allowance in §54.1-3408.4; reference to nonresident pharmacies in §54.1-3434.1; and reference in §54.1-3457.

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Current as of November 20, 2013.
For the most up-to-date listing of Board of Pharmacy contacts, visit *www.nabp.net*.

Glossary of Acronyms

AAS – Associate of Applied Science

ACPE – Accreditation Council for Pharmacy Education

AES – Accreditation Evaluation Service

ANP – Advanced Nurse Practitioner

APN – Advanced Practice Nurse

APRN – Advanced Practice Registered Nurse

ARNP – Advanced Registered Nurse Practitioner

ASHP – American Society of Health-System Pharmacists

CCAPP – Canadian Council for Accreditation of Pharmacy Programs

CE – Continuing Education

CEU – Continuing Education Unit

CFR – Code of Federal Regulations

CME – Continuing Medical Education

CNM – Certified Nurse Midwife

CNS – Clinical Nurse Specialist

CPE – Continuing Pharmacy Education

CRF – Compliance Resolution Fund

CRNA – Certified Nurse Anesthetist

DDS/DMD – Doctor of Dental Surgery/Medicine

DEA – Drug Enforcement Administration

DO – Doctor of Optometry

DPM – Doctor of Podiatric Medicine

DPS – Drug Product Substitution

DVM – Doctor of Veterinary Medicine

EPA – Environmental Protection Agency

ExCPT – Exam for the Certification of Pharmacy Technicians

FDA – Food and Drug Administration

FPGEC® – Foreign Pharmacy Graduate Examination Committee™

FPGEE® – Foreign Pharmacy Graduate Equivalency Examination®

GAV – Gross Annual Volume

HMO – Health Maintenance Organization

Glossary of Acronyms (cont.)

LAP – Licensee Assistance Program

LTCF – Long-Term Care Facility

MD – Doctor of Medicine

MPJE® – Multistate Pharmacy Jurisprudence Examination®

NABP® – National Association of Boards of Pharmacy®

NABP*LAW*® – NABP's national database of state pharmacy laws and regulations

NABPLEX® – National Association of Boards of Pharmacy Licensure Examination™

NAPLEX® – North American Pharmacist Licensure Examination®

NCCA – National Commission for Certifying Agencies

ND – Naturopathic Doctor

NP – Nurse Practitioner

NPLEx – National Precursor Log Exchange

OB/GYN – Obstetrician/Gynecologist

OTC – Over-the-Counter

PA – Physician Assistant

PBM – Pharmacy Benefits Management

PIC – Pharmacist-in-Charge

PILAR® – Pharmacist Intern License and Registration℠

PRN – As needed *(pro re nata)*

PTCB – Pharmacy Technician Certification Board

RMOP – Remote Medication Order Processing

RN – Registered Nurse

RPh – Registered Pharmacist

Rx – Prescription

TOEFL® – Test of English as a Foreign Language™

TOEFL iBT® – Test of English as a Foreign Language Internet-based Test

TSE® – Test of Spoken English

USP – United States Pharmacopeial Convention

USP–NF – United States Pharmacopeia–National Formulary

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Preamble and Mission Statement of the National Association of Boards of Pharmacy

Preamble

The National Association of Boards of Pharmacy (NABP) recognizes and supports pharmacists serving as the health care professionals responsible for providing patient care that ensures optimal medication therapy outcomes. NABP also recognizes the ongoing and critical need for patients' medications to be managed by a licensed pharmacist and state regulatory agencies to aggressively enforce standards of care.

NABP Mission Statement

NABP is the independent, international, and impartial Association that assists its member boards and jurisdictions in developing, implementing, and enforcing uniform standards for the purpose of protecting the public health.

NABP Member Boards of Pharmacy

Alabama State Board of Pharmacy
Alaska Board of Pharmacy
Arizona State Board of Pharmacy
Arkansas State Board of Pharmacy
California State Board of Pharmacy
Colorado State Board of Pharmacy
Connecticut Commission of Pharmacy
Delaware State Board of Pharmacy
District of Columbia Board of Pharmacy
Florida Board of Pharmacy
Georgia State Board of Pharmacy
Guam Board of Examiners for Pharmacy
Hawaii State Board of Pharmacy
Idaho State Board of Pharmacy
Illinois Department of Financial and Professional Regulation, Division of Professional Regulation – State Board of Pharmacy
Indiana Board of Pharmacy
Iowa Board of Pharmacy
Kansas State Board of Pharmacy
Kentucky Board of Pharmacy
Louisiana Board of Pharmacy
Maine Board of Pharmacy
Maryland Board of Pharmacy
Massachusetts Board of Registration in Pharmacy
Michigan Board of Pharmacy
Minnesota Board of Pharmacy
Mississippi Board of Pharmacy
Missouri Board of Pharmacy
Montana Board of Pharmacy
Nebraska Department of Health and Human Services, Division of Public Health, Licensure Unit
Nevada State Board of Pharmacy
New Hampshire Board of Pharmacy
New Jersey State Board of Pharmacy
New Mexico Board of Pharmacy
New York State Board of Pharmacy
North Carolina Board of Pharmacy
North Dakota State Board of Pharmacy
Ohio State Board of Pharmacy
Oklahoma State Board of Pharmacy
Oregon State Board of Pharmacy
Pennsylvania State Board of Pharmacy
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Rhode Island Board of Pharmacy
South Carolina Department of Labor, Licensing, and Regulation – Board of Pharmacy
South Dakota State Board of Pharmacy
Tennessee Board of Pharmacy
Texas State Board of Pharmacy
Utah Board of Pharmacy
Vermont Board of Pharmacy
Virgin Islands Board of Pharmacy
Virginia Board of Pharmacy
Washington State Pharmacy Quality Assurance Commission
West Virginia Board of Pharmacy
Wisconsin Pharmacy Examining Board
Wyoming State Board of Pharmacy

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How Pharmacists Keep Cash That Could Be Yours on Each Generic Prescription

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Last Updated May 27, 2011 12:51 PM EDT

Having your prescription filled with a cheap generic drug rather than a more expensive brand is supposed to be good for your wallet (they're cheaper) and good for the nation (by lowering the overall cost of healthcare). But **CVS**, **Walgreens** (WAG), **Kmart**, **Kroger** (KR) and **Target** (TGT) have found a way to line their own pockets in the process, according to a lawsuit filed by the attorney general of West Virginia.

Almost all states have laws encouraging generic substitution at the pharmacy. If your doctor prescribes the cholesterol drug **Zocor**, for instance, your pharmacist is supposed to ask you if it's OK to fill the scrip with generic **simvastatin**. It's the same drug, and the white coat behind the counter is supposed to tell you how much money you'll save by doing so.

West Virginia took its law a step further, and required pharmacies to pass on to patients the savings they make by going generic.

But West Virginia attorney general **Darrell McGraw** noticed that in the annual reports of CVS and Walgreens, the companies claimed they actually made more profit when they sold generics than when they sold brands. CVS's 2007 annual report says (see page 8):

> Although their lower prices depress revenue growth and we continue to see pressure on pharmacy reimbursement rates, generics are more profitable than brand name drugs and help drive margin expansion.
>
> In addition, we continued to benefit from the increased utilization of generic drugs (which normally yield a higher gross profit rate than equivalent brand name drugs) in both the Retail Pharmacy and Pharmacy Services segments.

Walgreens made a similar claim in its 2008 annual report:

> Overall margins were ... partially offset by an improvement in retail pharmacy margins, which were positively influenced by generic drug sales, ... Retail pharmacy margins increased as a result of growth in generic drug sales.

Savings not passed on

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Under West Virginia's law, pharmacies can't possibly make more money on generics than brands because the savings are supposed to be passed to the consumer. The West Virginia suit gives this hypothetical example:

Branded drug Pharmacy's acquisition cost: $64.76
Pharmacy's price to consumer: $96.09
Profit: $31.33

Generic drug Pharmacy's acquisition cost: $7.20
Pharmacy's price to consumer: $56.59
Profit: $49.39

Pharmacy's price to consumer had the pharmacy been following the law: $38.53 (i.e. $31.33 plus $7.20).

Thus the consumer loses $18.06 (the difference between the "legal" price of $38.53 and the actual price of $56.50) every time they fill a generic prescription.

CVS *et al.* claim the suit should be thrown out because it doesn't contain a specific concrete example of this ever happening; West Virginia recently won federal appeals court ruling allowing the case to proceed, which may produce those records in discovery.

In states other than Virginia, making larger profits on cheaper drugs and failing to pass on the savings is completely legal. In theory, those profits ought not to occur because pharmacies should be competing on price. If a store can acquire a pill for as little as $7.20, prices ought to fall quickly toward that level in a race to the bottom. But, as the Wall Street Journal discovered in 2007, prices don't fall that far.

Why might that be? It's interesting that *both* CVS and Walgreens noted in their annual reports that the source of their gross margin increases were generic drugs. This was not a mandatory disclosure. A conspiracy theorist might suggest that this is an example of "signalling"; the practice of drawing your competitor's attention to the fact that if you both refrain from getting into a price war you can both keep prices and margins high.

This is perfectly legal as long as neither company overtly cooperates with the other. That, surely, can't be the explanation for the amazing coincidence of both companies making higher profits on cheaper drugs. Can it?

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